GENERAL REVIEW

UDC: 616.127-005.8:[612.352:616.379-008.64
DOI: 10.2298/VSP121103017K

Stress hyperglycemia in acute myocardial infarction

Stres hiperglikemija u akutnom infarktu miokarda

Goran Koraćević*, Sladjana Vasiljević†, Radmila Veličković-Radovanović‡, Dejan Sakač§, Slobodan Obradović‖¶, Miodrag Damjanović*, Nebojša Krstić*, Marija Zdravković, Tomislav Kostić***

***Department of Cardiovascular Diseases, Clinical Center, Medical Faculty, University of Niš, Niš, Serbia; †Department of Anesthesiology and Intensive Care, Institute for Mother and Child Health Care of Serbia "Dr Vukan Čupić", Belgrade, Serbia; ‡Medical Faculty, University of Niš, Niš, Serbia; §Institute of Cardiovascular Diseases of Vojvodina, Sremska Kamenica, Serbia; ‖Clinic of Emergency Internal Medicine, Military Medical Academy, Belgrade, Serbia; ¶Faculty of Medicine of the Military Medical Academy, University of Defence, Belgrade, Serbia; **Department of Cardiology, University Hospital Medical Center "Bežanijska kosa", Faculty of Medicine, University of Belgrade, Belgrade, Serbia**

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

Ključne reči:
infarkt miokarda; glukoza u krvi; hiperglikemija; dijabetes melitus; mortalitet.

Introduction

Hyperglycemia as a response to stress was firstly described by a French physiologist Claude Bernard in 1855 [1]. 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 [2–7]. 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 [1–14]. 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 [14]. 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 [14].

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, a large-scale prospective study of patients with ST-Elevation Myocardial Infarction (STEMI), 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) [15]. In the retrospective study of 4176 patients without known DM undergoing primary PCI for STEMI, Timmer et al. [16] 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. [17] 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 [18] which, assessed by cardiovascular magnetic resonance (CMR), is an independent predictor of clinical outcome [19]. 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 [20]. High glycaemia on admission predicted increased in-hospital and long-term mortality in patients with STEMI complicated with cardiogenic shock [21]. Importance of SH seem to last for a very long time – even for decades, as demonstrated in the study od Deckers et al. [22]. 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),

Correspondence to: Goran P. Koraćević, Bul. Dr Z. Djindjića 48, Niš 18 000, Serbia; Phone: +381 185 33 644.
E-mail: gkoracevic@yahoo.com

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 preinvasive era (*p* value for heterogeneity of effects < 0.001) [23].

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 cardiorespiratory 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 [30]. Besides associations with VT/VF and AF, Dziewierz et al. [31]. demonstrated a connection of admission glycemia and second to third grade atriventricular (AV) block and pulmonary edema in patients with AMI [31]. 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. [33] recently evaluated the association of glucose level and clinical variables during primary PCI in patients with STEMI. They demonstrated that corrected thrombolysis 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 [35]. Additionally, SH correlates significantly with microalbuminuria, which is a sign of endothelial dycfunction [36].

Indeed, nothing in the organism is just black or white, paricularly 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-

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 glucoregulation. 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 Reciever 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 mmo/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) [43].

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. [45], 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-k β) [50] and promoting the procoagulant state [51, 52]. Recent studies show that TNF-alpha-induced activation of the NF-k β 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 [48].

Futher, 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 Ca^{2+}-ATPase (SERCA) and consequently abnormal Ca^{2+} signaling and contractile dysfunction [58].

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 [59].

Futhermore, acute hyperglycemia abolishes ischemic preconditioning *in vivo* [60].

Putative pathophysiologic mechanisms of stress hyperglycemia effects on worsening the prognosis and the occurence 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]?

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 exsisting myocardial damage), and increased catecholamine and sympatethic 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 determinats 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 bood 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.).

Microvascular obstruction was considered the reasonable explanation for the findings on contrast-enhanced cardiovascular magnetic resonance (CMR) [69]. SH is associated with a higher incidence of TIMI < 3 flow in the infarct-related artery after PCI [25] and even in patients with TIMI 3 flow after PCI patients with SH have higher final TIMI frame counts on angiography [70]; endothelial dysfunction [67]; no-reflow phenomenon", for which glycemia was the strongest independent predictor [67, 71]; decrease of collateral blood flow to the ischemic area (by adversely affecting nitric oxide availability) [67, 70]; electrophysiologic disturbances, resulting in arrhythmias [72, 73]; exaggeration of the inflammation by the oxidative mechanism [49, 71, 74]. For example, in-stent restenosis correlated with mean glycemia as well as with oxidative stress and inflammatory markers during the insulin infusion period and intensive glycemic control during PCI halved restenosis at 6 months [75], increased immune response [48, 73], increased apoptosis [61, 67], increase of interstitial fibrosis [61].

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 [63, 67], which results in part from diminished plasma fibrinolytic activity and effect of tissue plasminogen activator [63]. Also, glycemia is an independent predictor of platelet dependent thrombosis [70]. Moreover, among diabetic patients, those with STEMI and glycemia > 8.5 mmol/L on admission had a poorer response to clopidogrel [76]. Additionally, improved glycemic control reduces platelet reactivity in DM patients after PCI [68]. From therapeutic point of view, it may be important that in ACS patients with hyperglycemia intensive glucose control results in a reduction of platelet reactivity only in the presence of elevated HbA1c levels [77]; decreased nitric oxide bioavailability [78]; possible increased risk for upper gastrointestinal bleeding [79] 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 [80].

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 comapred 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 [81].

Stress hyperglycemia 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 [82–84]. 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 [15]. 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 MACCE (composite of death, reinfarction, stroke, or rehospitalization), adjusted OR 1.31, 95% CI 1.00 to 1.71, $p < 0.0001$ [25].

Tamita et al. [62] studied 275 AMI patients, with the median follow-up interval of 5.3 years. Patients with abnormal fasting glycemia 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 [62].

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) [85].

In the study of Mather et al. [86] patients with high admission glycemia 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) [86].

Zhang et al. [84] 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 [87].

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 glycemia [88].

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 [89, 90].

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) [91].

Mrdovic et al. [92] incorporated SH in the RISK-PCI score. SH was defined as glycemia ≥ 6.6 mmol/L at admisssion. 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 [92].

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 glycemia 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 hyperglycemia 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 lad to improved outcome compared with tolerating hyperglycemia 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 glycaemic 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].

Glucontrol (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 planed because the incidence of hypoglycemia (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 pateints. 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, 104]. The oposite results of the two major trials concerning this topic might be the consequence of suboptimal quality of studies [96].

The Hyperglycemia: 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 glycemia and high morbidity and mortality in AMI is not definitively confirmed, and hyperglycemia might be an epiphenomenon. Conclusive, large trials seem to be very expensive, precluding their conduction in conterporary economic environment – in the sufficent 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 hypoglycemia [69]. Recent meta-regression anlysis 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 optimaly 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 treshold, targets and means to treat hyperglycemia 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 [110–112].

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-

genic shock in STEMI patients [67]. Thus, GIK infusions are not recommended in current clinical guidelines [110]. 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. Regretably, there was no improvement in 30-day survival [113].

Importance of hypoglycemia, including iatrogenic one

An association of increased mortality and morbidity with hypoglycemia also has been demonstrated [40, 103, 114].

In a recent meta-regression analysis (which involved 2,113 patients), Chatterjee et al. [106] 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 3.69–48.61; $p < 0.01$), 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 [106]. Hypoglycemia relates to prolonged hospital, greater cost of hospitalization, and higher mortality both during hospitalization, and after discharge [115]. Several mechanisms may contribute. For example, hypoglycaemia may exacerbate myocardial ischaemia and may cause dysrhythmias [115, 116]. Hypoglycemic episodes provoke sympathetic nervous system activation and catecholamine surge, leading to arrhythmia, myocardial ischemia, and sudden death. Hypoglycemia can be particularly dangerous in pateints with cardiac autonomic neuropathy [117]. Hypoglycemia is related to prolongation of QT and reentrant arrhythmias, often quoted as crucial for the "dead in bed" syndrome [114]. Too rapid rate of glycemia reduction could be a factor in adverse CVD outcomes [117]. 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 [118]. Spontaneous hypoglycemia, may be even more dangerous than iatrogenic hypoglycemia [119]. 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 [118]. 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 [88].

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 glycemia measurement. Thus, both in anemic and in hypoxic patients, falsely high glycemia readings may occur [120].

Recently, a new, promissing therapeutic approach for hyperglycemia was proposed, namely, glucagon-like peptide infusion, which exerts insulinotropic and insulinomimetic actions, with a low risk for hypoglycemia [73, 121, 122].

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) [110]. A well-designed RCT in ACS is obviously needed to determine glucose treatment thresholds and targets [102]. 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 glycemia in NSTE-ACS from a more stringent to a more moderate target range, and to avoid hypoglycemia [102]. 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 [123]. 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) [110]. 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 (140–180mg/dl) [96, 124].

Targets for hyperglycemia therapy

Guidelines for ACS recommend nowdays 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)] [103].

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 [94, 107]. 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 [102]. The recommended blood glucose target is 7.7–10 mmol/L (140–180 mg/dL) for most patients [123].

More recent guidelines recommend a more lax control of glycemia in critically ill patients: between 8–10 mmol/L (144–180 mg/dL) [125].

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 advices for other hospitalized pateints. 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 recomended 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 writen 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 stil 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 infarctiion patients

DM is another characteristic associated with high risk for adverse outcomes after ACS [102]. For adequate treatment, it is important do 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 hyperglycaemia 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 cut-offs 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

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.

R E F E R E N C E S

1. *Bernard C.* Lessons from experimental physiology applied to the medicine. Paris: Balliere; 1855. p. 296−313. (French)
2. *Johan Groeneveld AB, Beishuizen A, Visser FC.* Insulin: a wonder drug in the critically ill? Crit Care 2002; 6(2): 102−5.
3. *Gearhart MM, Parbhoo SK.* Hyperglycemia in the critically ill patient. AACN Clin Issues 2006; 17(1): 50−5.
4. *van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M,* et al. Intensive insulin therapy in the critically ill patients. N Engl J Med 2001; 345(19): 1359−67.
5. *McCowen KC, Malhotra A, Bistrian BR.* Stress-induced hyperglycemia. Crit Care Clin 2001; 17(1): 107−24.
6. *Nasraway SA Jr.* Hyperglycemia during critical illness. JPEN J Parenter Enteral Nutr 2006; 30(3): 254−8.
7. *Koraćević G, Petrović S, Tomašević M, Apostolović S, Damjanović M.* Stress hyperglycemia in acute myocardial infarction. Facta Universitatis (Medicine and Biology) 2006; 13(3): 152−7.
8. *Stubbs PJ, Laycock J, Alaghband-Zadeh J, Carter G, Noble MI.* Circulating stress hormone and insulin concentrations in acute coronary syndromes: Identification of insulin resistance on admission. Clin Sci (Lond) 1999; 96(6): 589−95.
9. *Van Cromphaut SJ.* Hyperglycaemia as part of the stress response: the underlying mechanisms. Best Pract Res Clin Anaesthesiol 2009; 23(4): 375−86.
10. *Langouche L, van den Berghe G.* The dynamic neuroendocrine response to critical illness. Endocrinol Metab Clin North Am 2006; 35(4): 777−91.
11. *van den Berghe G.* Neuroendocrine pathobiology of chronic critical illness. Crit Care Clin 2002; 18(3): 509−28.
12. *Grimble RF.* Inflammatory status and insulin resistance. Curr Opin Clin Nutr Metab Care 2002; 5(5): 551−9.
13. *Marik PE, Raghavan M.* Stress-hyperglycemia, insulin and immunomodulation in sepsis. Intensive Care Med 2004; 30(5): 748−56.
14. *Koracevic GP.* The consensus is clearly needed for the definition of stress hyperglycaemia in acute myocardial infarction. Eur Heart J 2007; 28(16): 2042.
15. *Planer D, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Xu K,* et al. Impact of hyperglycemia in patients with ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention: The HORIZONS-AMI trial. Int J Cardiol 2013; 167(6): 2572−9.
16. *Timmer JR, Hoekstra M, Nijsten MW, Horst IC, Ottervanger JP, Slingerland RJ,* et al. Prognostic value of admission glycosylated hemoglobin and glucose in nondiabetic patients with ST-segment-elevation myocardial infarction treated with percutaneous coronary intervention. Circulation 2011; 124(6): 704−11.
17. *Mladenović V, Zdravković V, Jović M, Vucić R, Irić-Cupić V, Rosić M.* Influence of admission plasma glucose level on short- and long-term prognosis in patients with ST-segment elevation myocardial infarction. Vojnosanit Pregl 2010; 67(4): 291−5.
18. *Teraguchi I, Imanishi T, Ozaki Y, Tanimoto T, Kitabata H, Ino Y,* et al. Impact of stress hyperglycemia on myocardial salvage following successfully recanalized primary acute myocardial infarction. Circ J 2012; 76(11): 2690−6.
19. *Eitel I, Desch S, Fuernau G, Hildebrand L, Gutberlet M, Schuler G,* et al. Prognostic significance and determinants of myocardial salvage assessed by cardiovascular magnetic resonance in acute reperfused myocardial infarction. J Am Coll Cardiol 2010; 55(22): 2470−9.
20. *Stojković A, Koracević G, Perisić Z, Krstić N, Pavlović M, Todorović L,* et al. The influence of stress hyperglycemia on the prognosis of patients with acute myocardial infarction and temporary electrical cardiac pacing. Srp Arh Celok Lek 2010; 138(7−8): 430−5. (Serbian)
21. *Pres D, Gasior M, Strojek K, Gierlotka M, Hawranek M, Lekston A,* et al. Blood glucose level on admission determines in-hospital and long-term mortality in patients with ST-segment elevation myocardial infarction complicated by cardiogenic shock treated with percutaneous coronary intervention. Kardiol Pol 2010; 68(7): 743−51.
22. *Deckers JW, van Domburg RT, Akkerhuis M, Nauta ST.* Relation of Admission Glucose Levels, Short- and Long-Term (20-Year) Mortality After Acute Myocardial Infarction. Am J Cardiol 2013; 112(9): 1306−10.
23. *de Mulder M, Cornel J, Ploeg T, Boersma E, Umans VA.* Elevated admission glucose is associated with increased long-term mortality in myocardial infarction patients, irrespective of the initially applied reperfusion strategy. Am Heart J 2010; 160(3): 412−9.
24. *Ladeira RT, Baracioli LM, Faulin TE, Abdalla DS, Seydell TM, Maranhão RC,* et al. Unrecognized diabetes and myocardial necrosis: predictors of hyperglycemia in myocardial infarction. Arq Bras Cardiol 2013; 100(5): 404−11.
25. *Naber CK, Mehta RH, Jünger C, Zeymer U, Wienbergen H, Sabin GV,* et al. Impact of admission blood glucose on outcomes of nondiabetic patients with acute ST-elevation myocardial infarction (from the German Acute Coronary Syndromes [ACOS] Registry). Am J Cardiol 2009; 103(5): 583−7.
26. *Chen J, Tseng C, Tsai S, Chiu W.* Initial serum glucose level and white blood cell predict ventricular arrhythmia after first acute myocardial infarction. Am J Emerg Med 2010; 28(4): 418−23.
27. *Sanjuan R, Blasco ML, Martinez-Maicas H, Carbonell N, Miñana G, Nuñez J,* et al. Acute myocardial infarction: high risk ventricular tachyarrhythmias and admission glucose level in patients with and without diabetes mellitus. Curr Diabetes Rev 2011; 7(2): 126−34.
28. *Oliver MF, Opie LH.* Effects of glucose and fatty acids on myocardial ischaemia and arrhythmias. Lancet 1994; 343(8890): 155−8.
29. *Oliver MF.* Metabolic causes and prevention of ventricular fibrillation during acute coronary syndromes. Am J Med 2002; 112(4): 305−11.
30. *Koracevic GP, Petrovic S, Damjanovic MR, Stanojlovic T.* Association of stress hyperglycemia and atrial fibrillation in myocardial infarction. Wien Klin Wochenschr 2008; 120(13−14): 409−13.
31. *Dziewierz A, Giszterowicz D, Siudak Z, Rakowski T, Dubiel JS, Dudek D.* Admission glucose level and in-hospital outcomes

in diabetic and non-diabetic patients with acute myocardial infarction. Clin Res Cardiol 2010; 99(11): 715−21.
32. *Sanjuán R, Núñez J, Blasco ML, Miñana G, Martínez-Maicas H, Carbonell N,* et al. Prognostic implications of stress hyperglycemia in acute ST elevation myocardial infarction. Prospective observational study. Rev Esp Cardiol 2011; 64(3): 201−7.
33. *Nakamura T, Ako J, Kadowaki T, Funayama H, Sugawara Y, Kubo N*, et al. Impact of acute hyperglycemia during primary stent implantation in patients with ST-elevation myocardial infarction. J Cardiol 2009; 53(2): 272−7.
34. *Timmer JR, Ottervanger JP, de Boer MJ, Dambrink JH, Hoorntje JC, Gosselink AT,* et al. Hyperglycemia is an important predictor of impaired coronary flow before reperfusion therapy in ST-segment elevation myocardial infarction. J Am Coll Cardiol 2005; 45(7): 999−1002.
35. *Djordjevic-Radojkovic D, Koracevic G, Stanojevic D, Damjanovic M, Apostolovic S, Pavlovic M.* Stress hyperglycemia in acute ST-segment elevation myocardial infarction is a marker of left ventricular remodeling. Acute Card Care 2013; 15(2): 38−43.
36. *Stanojevic D, Apostolovic SR, Koracevic GP, Jankovic-Tomasevic R, Pavlovic M, Djordjevic-Radojkovic DD,* et al. Stress hyperglycemia as an indicator of in-hospital and 6 month prognosis in acute myocardial infarction and its correlation with endothelial dysfunction. Circulation 2012; 125(19): E861.
37. *Marik PE, Bellomo R.* Stress hyperglycemia: an essential survival response. Crit Care Med 2013; 41(6): e93−4.
38. *Deedwania P, Kosiborod M, Barrett E, Ceriello A, Isley W, Mazzone T*, et al. Hyperglycemia and acute coronary syndrome: a scientific statement from the American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation 2008; 117(12): 1610−9.
39. *Bhadriraju S, Ray KK, de Franco AC, Barber K, Bhadriraju P, Murphy SA,* et al. Association between blood glucose and long-term mortality in patients with acute coronary syndromes in the OPUS-TIMI 16 trial. Am J Cardiol 2003; 97(11): 1573−7.
40. *Pinto DS, Skolnick AH, Kirtane AJ, Murphy SA, Barron HV, Giugliano RP,* et al. U-shaped relationship of blood glucose with adverse outcomes among patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol 2005; 46(1): 178−80.
41. *Koracevic GP, Krstic NH, Damjanovic MR, Velickovic-Radovanovic RM, Apostolovic SR, Pavlovic S,* et al. Two different cut-off values for stress hyperglycemia in myocardial infarction. HealthMED 2012; 6(7): 2507−12.
42. *Koracevic GP.* Stress hyperglycemia -better prognosticator with different cut-offs. Am J Med 2013; 126(5): e9.
43. *Capes SE, Hunt D, Malmberg K, Gerstein HC.* Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: A systematic overview. Lancet 2000; 355(9206): 773−8.
44. *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): 758−60.
45. *Sewdarsen M, Vythilingum S, Jialal I, Becker PJ.* Prognostic importance of admission plasma glucose in diabetic and non-diabetic patients with acute myocardial infarction. Q J Med 1989; 71(265): 461−6.
46. *Choi SW, Benzie IF, Ma SW, Strain JJ, Hannigan BM.* Acute hyperglycemia and oxidative stress: direct cause and effect. Free Radic Biol Med 2008; 44(7): 1217−31.
47. *Ling P, Smith RJ, Bistrian BR.* Hyperglycemia enhances the cytokine production and oxidative responses to a low but not high dose of endotoxin in rats. Crit Care Med 2005; 33(5): 1084−9.
48. *Marfella R, Siniscalchi M, Esposito K, Sellitto A, de Fanis U, Romano C,* et al. Effects of stress hyperglycemia on acute myocardial infarction: Role of inflammatory immune process in functional cardiac outcome. Diabetes Care 2003; 26(11): 3129−35.
49. *Esposito K, Nappo F, Marfella R, Giugliano G, Giugliano F, Ciotola M,* et al. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. Circulation 2002; 106(16): 2067−72.
50. *Iwasaki Y, Kambayashi M, Asai M, Yoshida M, Nigawara T, Hashimoto K.* High glucose alone, as well as in combination with proinflammatory cytokines, stimulates nuclear factor kappa-B-mediated transcription in hepatocytes in vitro. J Diabetes Complications 2007; 21(1): 56−62.
51. *Perner A, Nielsen SE, Rask-Madsen J.* High glucose impairs superoxide production from isolated blood neutrophils. Intensive Care Med 2003; 29(4): 642−5.
52. *Nielson CP, Hindson DA.* Inhibition of polymorphonuclear leukocyte respiratory burst by elevated glucose concentrations in vitro. Diabetes 1989; 38(8): 1031−5.
53. *Dhingra S, Sharma AK, Arora RC, Slezak J, Singal PK.* IL-10 attenuates TNF-alpha-induced NF kappaB pathway activation and cardiomyocyte apoptosis. Cardiovasc Res 2009; 82(1): 59−66.
54. *Nizamutdinova IT, Guleria RS, Singh AB, Kendall JA, Baker KM, Pan J.* Retinoic acid protects cardiomyocytes from high glucose-induced apoptosis through inhibition of NF-κB signaling pathway. J Cell Physiol 2013; 228(2): 380−92.
55. *Cai L, Li W, Wang G, Guo L, Jiang Y, Kang JY.* Hyperglycemia-induced apoptosis in mouse myocardium: mitochondrial cytochrome C-mediated caspase-3 activation pathway. Diabetes 2002; 51(6): 1938−48.
56. *Risso A, Mercuri F, Quagliaro L, Damante G, Ceriello A.* Intermittent high glucose enhances apoptosis in human umbilical vein endothelial cells in culture. Am J Physiol Endocrinol Metab 2001; 281: 924−930.
57. *Stegenga ME, Crabben SN, Levi M, de Vos AF, Tanck MW, Sauerwein HP*, et al. Hyperglycemia stimulates coagulation, whereas hyperinsulinemia impairs fibrinolysis in healthy humans. Diabetes 2006; 55(6): 1807−12.
58. *Tang WH, Cheng WT, Kravtsov GM, Tong XY, Hou XY, Chung SK*, et al. Cardiac contractile dysfunction during acute hyperglycemia due to impairment of SERCA by polyol pathway-mediated oxidative stress. Am J Physiol Cell Physiol 2010; 299(3): C643−53.
59. *Nieuwdorp M, van Haeften TW, Gouverneur MC, Mooij HL, Lieshout MH, Levi M*, et al. Loss of endothelial glycocalyx during acute hyperglycemia coincides with endothelial dysfunction and coagulation activation in vivo. Diabetes 2006; 55(2): 480−6.
60. *Kersten JR, Schmeling TJ, Orth KG, Pagel PS, Warltier DC.* Acute hyperglycemia abolishes ischemic preconditioning in vivo. Am J Physiol 1998; 275(2 Pt 2): H721−5.
61. *Lazaros G, Tsiachris D, Vlachopoulos C, Chrysohoou C, Milkas A, Papageorgiou N,* et al.. Distinct association of admission hyperglycemia with one-year adverse outcome in diabetic and non-diabetic patients with acute ST-elevation myocardial infarction. Hellenic J Cardiol 2013; 54(2): 119−25.
62. *Tamita K, Katayama M, Takagi T, Yamamuro A, Kaji S, Yoshikawa J*, et al. Newly diagnosed glucose intolerance and prognosis after acute myocardial infarction: comparison of post-challenge versus fasting glucose concentrations. Heart 2012; 98(11): 848−54.
63. *Pinheiro CP, Oliveira MD, Faro GB, Silva EC, Rocha EA, Barreto-Filho JA,* et al. Prognostic value of stress hyperglycemia for in-hospital outcome in acute coronary artery disease. Arq Bras Cardiol 2013; 100(2): 127−34.

64. *Marfella R, Verrazzo G, Acampora R, la Marca C, Giunta R, Lucarelli C*, et al. Glutathione reverses systemic hemodynamic changes by acute hyperglycaemia in healthy subjects. Am J Physiol 1995; 268 (6 Pt 1): E1167−73.
65. *Takada JY, Ramos RB, Roza LC, Avakian SD, Ramires JA, Mansur AP*. In-hospital death in acute coronary syndrome was related to admission glucose in men but not in women. Cardiovasc Diabetol 2012; 11: 47.
66. *Ishihara M, Inoue I, Kawagoe T, Shimatani Y, Kurisu S, Nishioka K,* et al. Impact of acute hyperglycemia on left ventricular function after reperfusion therapy in patients with a first anterior wall acute myocardial infarction. Am Heart J 2003;146(4): 674−8.
67. *Ishihara M*. Acute hyperglycemia in patients with acute myocardial infarction. Circ J 2012; 76(3): 563−71.
68. *Singla A, Orshaw P, Boura J, Harjai KJ*. Glycosylated hemoglobin and outcomes in diabetic patients with acute myocardial infarction after successful revascularization with stent placement: findings from the guthrie health off-label stent (GHOST) investigators. J Interv Cardiol 2012; 25(3): 262−9.
69. *Jensen CJ, Eberle HC, Nassenstein K, Schlosser T, Farazandeh M, Naber CK,* et al. Impact of hyperglycemia at admission in patients with acute ST-segment elevation myocardial infarction as assessed by contrast-enhanced MRI. Clin Res Cardiol 2011; 100(8): 649−59.
70. *Ege M, Güray U, Güray Y, Yılmaz MB, Demirkan B, Saşmaz A,* et al. Relationship between TIMI frame count and admission glucose values in acute ST elevation myocardial infarction patients who underwent successful primary percutaneous intervention. Anadolu Kardiyol Derg 2011; 11(3): 213−7.
71. *Iwakura K, Ito H, Ikushima M, Kawano S, Okamura A, Asano K,* et al. Association between hyperglycemia and the no-reflow phenomenon in patients with acute myocardial infarction. J Am Coll Cardiol 2003; 41(1): 1−7.
72. *Marfella R, Nappo F, De Angelis L, Siniscalchi M, Rossi F, Giugliano D*. The effect of acute hyperglycaemia on QTc duration in healthy man. Diabetologia 2000; 43(5): 571−5.
73. *Hoebers LP, Damman P, Claessen BE, Vis MM, Baan J, Straalen JP,* et al. Predictive value of plasma glucose level on admission for short and long term mortality in patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. Am J Cardiol 2012; 109(1): 53−9.
74. *Ceriello A*. Acute hyperglycaemia and oxidative stress generation. Diabet Med 1997; 14(Suppl 3): S45−9.
75. *Marfella R, Sasso FC, Siniscalchi M, Paolisso P, Rizzo MR, Ferraro F,* et al. Peri-procedural tight glycemic control during early percutaneous coronary intervention is associated with a lower rate of in-stent restenosis in patients with acute ST-elevation myocardial infarction. J Clin Endocrinol Metab 2012; 97(8): 2862−71.
76. *Kuliczkowski W, Gąsior M, Pres D, Kaczmarski J, Greif M, Łaszewska A,* et al.. Effect of glycemic control on response to antiplatelet therapy in patients with diabetes mellitus and ST-segment elevation myocardial infarction. Am J Cardiol 2012; 110(3): 331−6.
77. *Vivas D, García-Rubira JC, Bernardo E, Angiolillo DJ, Martín P, Calle-Pascual A,* et al. Influence of HbA1c levels on platelet function profiles associated with tight glycemic control in patients presenting with hyperglycemia and an acute coronary syndrome. A subanalysis of the CHIPS Study. J Thromb Thrombolysis 2013; 35(2): 165−74.
78. *Li D, Hua Q, Guo J, Li H, Chen H, Zhao S*. Admission glucose level and in-hospital outcomes in diabetic and non-diabetic patients with ST-elevation acute myocardial infarction. Intern Med 2011; 50(21): 2471−5.
79. *Liao WI, Sheu WH, Chang WC, Hsu CW, Chen YL, Tsai SH*. An Elevated Gap between Admission and A1C-Derived Average Glucose Levels Is Associated with Adverse Outcomes in Diabetic Patients with Pyogenic Liver Abscess. PLoS One 2013; 8(5): e64476.
80. *Laine L, Takeuchi K, Tarnawski A*. Gastric mucosal defense and cytoprotection: bench to bedside. Gastroenterology 2008; 135(1): 41−60.
81. *Giraldez RR, Clare RM, Lopes RD, Dalby AJ, Prabhakaran D, Brogan GX,* et al. Prevalence and clinical outcomes of undiagnosed diabetes mellitus and prediabetes among patients with high-risk non-ST-segment elevation acute coronary syndrome. Am Heart J 2013; 165(6): 918−25.
82. *ShaoNan L, GuangLian L, XiaoMing L, Zhen L, KaiWei F, Jian L,* et al. The relationship between stress-induced hyperglycemia and myocardial ischemia-reperfusion injury in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention. Chinese J Pract Intern Med 2009; 29(12): 1126−29.
83. *Eitel I, Hintze S, de Waha S, Fuernau G, Lurz P, Desch S,* 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 Imaging 2012; 5(6): 708−18.
84. *Zhang J, Zhou Y, Cao S, Yang Q, Yang S, Nie B*. Impact of stress hyperglycemia on in-hospital stent thrombosis and prognosis in nondiabetic patients with ST-segment elevation myocardial infarction undergoing a primary percutaneous coronary intervention. Coron Artery Dis 2013; 24(5): 352−6.
85. *Ergelen M, Uyarel H, Cicek G, Isik T, Osmonov D, Gunaydin ZY,* et al. Which is worst in patients undergoing primary angioplasty for acute myocardial infarction? Hyperglycaemia? Diabetes mellitus? Or both. Acta Cardiol 2010; 65(4): 415−23.
86. *Mather AN, Crean A, Abidin N, Worthy G, Ball SG, Plein S,* et al. Relationship of dysglycemia to acute myocardial infarct size and cardiovascular outcome as determined by cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2010; 12(1): 61.
87. *Sanjuán R, Núñez J, Blasco LM, Miñana G, Martínez-Maicas H, Carbonell N,* et al. Prognostic implications of stress hyperglycemia in acute ST elevation myocardial infarction. Prospective observational study. Rev Esp Cardiol 2011; 64(3): 201−7.
88. *Liu Y, Yang YM, Zhu J, Tan HQ, Liang Y, Li JD*. Haemoglobin A(1c) , acute hyperglycaemia and short-term prognosis in patients without diabetes following acute ST-segment elevation myocardial infarction. Diabet Med 2012; 29(12): 1493−500.
89. *Stolker JM, McCullough PA, Rao S, Inzucchi SE, Spertus JA, Maddox TM,* et al. Pre-procedural glucose levels and the risk for contrast-induced acute kidney injury in patients undergoing coronary angiography. J Am Coll Cardiol 2010; 55(14): 1433−40.
90. *Alpert MA, Carlino C*. Pre-procedural blood glucose levels: a new risk marker for contrast-induced acute kidney injury in patients without diabetes with acute myocardial infarction. J Am Coll Cardiol 2010; 55(14): 14413.
91. *GuoHong Y, Wang Wei W*. Predictive value of admission serum glucose level on hospitalized mortality in acute myocardial infarction after percutaneous coronary intervention. Biomed Engineering Clin Med 2009; 13(1): 31−3.
92. *Mrdovic I, Savic L, Krljanac G, Asanin M, Perunicic J, Lasica R,* et al. Predicting 30-day major adverse cardiovascular events after primary percutaneous coronary intervention. The RISK-PCI score. Int J Cardiol 2013; 162(3): 220−7.
93. *Pei-Chi C, Su-Kiat C, Huei-Fong H, Chung-Yen H, Chiu-Mei L, Shih-Ming* L, et al. Admission hyperglycemia predicts poorer

short- and long-term outcomes after primary percutaneous coronary intervention for ST-elevation myocardial infarction. J Diabetes Invest 2013; doi: 10.1111/jdi.12113.

94. *Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA,* et al. Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012; 33(20): 2569−619.
95. *Dhatariya K.* Should inpatient hyperglycaemia be treated. Br Med J 2013; 346: f134.
96. *Chandrasekara H, Brough C, Goenka N, Somauroo J, Hardy K.* Management of hyperglycaemia in people with acute coronary syndromes (NICE Clinical Guideline 130): uncertainty persists (pages 9-11). Pract Diabet 2012; 29(1): 7−37.
97. *Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I*, et al. Intensive insulin therapy in the medical ICU. N Engl J Med 2006; 354(5): 449−61.
98. *Van den Berghe G, Wilmer A, Milants I, Wouters PJ, Bouckaert B, Bruyninckx F*, et al. Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. Diabetes 2006; 55(11): 3151−9.
99. *Vlasselaers D, Milants I, Desmet L, Wouters PJ, Vanhorebeek I, van den Heuvel I*, et al. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. Lancet 2009; 373(9663): 547−56.
100. *Mesotten D, van den Berghe G.* Glycemic targets and approaches to management of the patient with critical illness. Curr Diab Rep 2012; 12(1): 101−7.
101. *Jneid H, Anderson JL, Wright RS, Adams CD, Bridges CR, Casey DE,* et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2012; 60(7): 645−81.
102. *Hamm CW, Bass JP, Agewall S, Bax J, Boersma E, Bueno H*, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2011; 32(23): 2999−3054.
103. *Malmberg K, Ryden L, Wedel H, Birkeland K, Bootsma A, Dickstein K,* et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. Eur Heart J 2005; 26(7): 650−61.
104. *Cheung NW, Wong VW, McLean M.* The Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study: a randomized controlled trial of insulin infusion therapy for myocardial infarction. Diabetes Care 2006; 29(4): 765−70.
105. *Chatterjee S, Sharma A, Lichstein E, Mukherjee D.* Intensive Glucose Control in Diabetics with an Acute Myocardial Infarction Does not Improve Mortality and Increases Risk of Hypoglycemia-A Meta-Regression Analysis. Curr Vasc Pharmacol 2013; 11(1): 100−4.
106. *Centre for Clinical Practice at NICE (UK).* Hyperglycaemia in Acute Coronary Syndromes: Management of Hyperglycaemia in People with Acute Coronary Syndromes. London: National Institute for Health and Clinical Excellence (UK); 2011.
107. *Malmberg K, Rydén L, Efendic S, Herlitz J, Nicol P, Waldenström A,* et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. J Am Coll Cardiol 1995; 26(1): 57−65.
108. *Diaz R, Goyal A, Mehta SR, Afzal R, Xavier D, Pais P*, et al. Glucose-insulin-potassium therapy in patients with ST-segment elevation myocardial infarction. JAMA 2007; 298(20): 2399−405.
109. *Vivas D, Bernardo E, Palacios-Rubio J, Fernández-Ortiz A.* How to manage hyperglycemia in an acute coronary syndrome patient. Curr Treat Options Cardiovasc Med 2013; 15(1): 93−103.
110. *Mehta SR, Yusuf S, Diaz R, Zhu J, Pais P, Xavier D*, et al. Effect of glucoseinsulin- potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. JAMA 2005; 293(4): 437−46.
111. *Timmer JR, Svilaas T, Ottervanger JP, Henriques JP, Dambrink JH, van den Broek SA*, et al. Glucoseinsulin- potassium infusion in patients with acute myocardial infarction without signs of heart failure: the Glucose-Insulin-Potassium Study (GIPS)-II. J Am Coll Cardiol 2006; 47(8): 1730−1.
112. *Selker HP, Beshansky JR, Sheehan PR, Massaro JM, Griffith JL, D'agostino RB,* et al. Out-of-hospital administration of intravenous glucose-insulin-potassium in patients with suspected acute coronary syndromes: the IMMEDIATE randomized controlled trial. JAMA 2012; 307(18): 1925-−33.
113. *Svensson AM, Mcguire DK, Abrahamsson P, Dellborg M.* Association between hyper- and hypoglycaemia and 2 year all-cause mortality risk in diabetic patients with acute coronary events. Eur Heart J 2005; 26: 1255−61.
114. *Nordin C.* The case for hypoglycaemia as a proarrhythmic event: basic and clinical evidence. Diabetologia 2010; 53(8): 1552−61.
115. *Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M*, et al. . Management of hyperglycaemia in type 2 diabetes: a patient- centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012; 55(6): 1577−96.
116. *Kishore P, Kim SH, Crandall JP.* Glycemic control and cardiovascular disease: what's a doctor to do. Curr Diab Rep 2012; 12(3): 255−64.
117. *Nusca A, Patti G, Marino F, Mangiacapra F, D'ambrosio A, Di Sciascio G.* Prognostic role of preprocedural glucose levels on short- and long-term outcome in patients undergoing percutaneous coronary revascularization. Catheter Cardiovasc Interv 2012; 80(3): 377−84.
118. *Korsiborod M, Inzucchi SE, Goyal A, Krumholz HM, Masoudi FA, Xiao L,* et al. Relationship between spontaneous and iatrogenic hypoglycemia and mortality in patients hospitalized with acute myocardial infarction. JAMA 2009; 301(15): 1556−64.
119. *Flower O, Finfer S.* Glucose control in critically ill patients. Intern Med J 2012; 42(1): 4−6.
120. *Timmers L, Henriques JP, de Kleijn DP, Devries JH, Kemperman H, Steendijk P,* et al. Exenatide reduces infarct size and improves cardiac function in a porcine model of ischemia and reperfusion injury. J Am Coll Cardiol 2009; 53(6): 501−10.
121. *Nikolaidis LA, Mankad S, Sokos GG, Miske G, Shah A, Elahi D,* et al. Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. Circulation 2004; 109(8): 962−5.
122. *Vergès B, Avignon A, Bonnet F, Catargi B, Cattan S, Cosson E,* et al. Consensus statement on the care of the hyperglycaemic/diabetic patient during and in the immediate follow-up of acute coronary syndrome. Diabetes Metab 2012; 38(2): 113−27.
123. *American Diabetes Association.* Standards of Medical Care in Diabetes - 2010. Diabetes Care 2010; 33(Suppl 1): S11−61.
124. *McGregor AK, Leech N, Purcell IF, Edwards R.* Effect of primary percutaneous coronary intervention on stress hypergly-

caemia in myocardial infarction. Diabet Med 2012; 29(10): 1317−20.

125. Scottish Intercollegiate Guidelines Network. Acute coronary syndromes (SIGN 116). 2011. [cited 2012 Feb 11]. Available from: www.sign.ac.uk/pdf/sign116.pdf
126. *Qaseem A, Humphrey LL, Chou R, Snow V, Shekelle P.* Use of intensive insulin therapyfor the management of glycemic control in hospitalized patients: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2011; 154(4): 260−7.
127. *O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos J*A, 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. Circulation 2013; 127(4): 362−425.
128. *Jacobi J, Bircher N, Krinsley J, Agus M, Braithwaite SS, Deutschman C,* et al. Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. Crit Care Med 2012; 40(12): 3251−76.
129. *Ye Y, Xie H, Zhao X, Zhang S*. The oral glucose tolerance test for the diagnosis of diabetes mellitus in patients during acute coronary syndrome hospitalization: a meta-analysis of diagnostic test accuracy. Cardiovasc Diabetol 2012; 11: 155.
130. *Rydén L, Standl E, Bartnik M, van den Berghe G, Betteridge J, de Boer MJ,* et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur Heart J 2007; 28(1): 88−136.
131. *Chakrabarti AK, Singh P, Gopalakrishnan L, Kumar V, Doherty EM, Abueg C*, et al. Admission hyperglycemia and acute myocardial infarction: outcomes and potential therapies for diabetics and nondiabetics. Cardiol Res Pract 2012; 2012: 704314.

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