Management of hyperglycemia during and in the immediate follow-up of acute coronary syndrome

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Diabetes is a serious, frequent, and insidious morbidity and mortality risk factor in patients with coronary artery disease. It has been shown that carbohydrate metabolism disorders are common in acute coronary syndromes (ACSs): 30–40% of patients have diabetes, 25–36% have an intolerance to carbohydrates, and only 30–40% have a normal carbohydrate profile. Hyperglycemia occurring either in diabetic or nondiabetic patients is strongly associated with a poor prognosis. It increases the extent of myocardial necrosis, and the risk of recurrence acute coronary syndrome and hemodynamic complications, particularly heart failure and cardiogenic shock, reflecting the importance of optimal management of glucose metabolism abnormalities. The objective of this article is to suggest a screening and management guide for carbohydrate metabolism disorders during and in the immediate follow-up of ACS in diabetic and nondiabetic patients. Screening must be systematic in any patient admitted for ACS, and based on hemoglobin A1c and oral glucose tolerance testing. Treatment of hyperglycemia in the cardiology intensive care unit is recommended in any patient admitted with hyperglycemia >1.80 g/L or postfeeding blood glucose level >1.40 g/L, and should be based on intravenous insulin with concomitant infusion of glucose solution under strict monitoring. Once the patient is no longer in intensive care, intravenous insulin therapy is no longer recommended, and the passage to a fixed insulin therapy regimen or to oral antidiabetics should be considered in consultation with diabetologists. During the rehabilitation phase, good glycemic control improves both prognosis and survival.

Keywords: Diabetes, Hyperglycemia, Acute coronary syndrome, Oral antidiabetics, Intravenous insulin therapy

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REVIEW ARTICLE

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1. Introduction

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia resulting from a defect of secretion or action of insulin, or a combination of both. We distinguish two types. Type 2 is the most common (95%), and is seen especially in individuals aged >40 years; it is characterized by resistance to insulin and/or insulin deficiency. Type 1 is less common, occurs at a young age and is characterized by absolute insulin deficiency [1].

However, hyperglycemia during stress situations, especially during acute coronary syndrome (ACS), may also be seen in nondiabetic patients. Regardless of whether the patient has diabetes, hyperglycemia is a predictive factor of survival and occurrence of complications. Karetnikova et al. [2] have demonstrated that there is a direct linear relationship between hyperglycemia levels and in-hospital mortality in patients admitted for myocardial infarction (MI), and that hyperglycemia affects the short and long-term prognosis in patients with or without diabetes mellitus [2]. Thus, good glycemic control may improve prognosis, but so far, recommendations for the management of glycemic disorders in the setting of ACS are limited.

In this article, based on data from the literature, we aim to clarify how to manage hyperglycemia during and in the immediate follow-up of ACS.

Abbreviations

ACS	Acute coronary syndrome
ACTH	Adrenocorticotrophic hormone
BG	Blood glucose
CRH	Corticotropin-releasing hormone
DPP-4	Dipeptidyl peptidase-4
FDS	Francophone Diabetes Society
FPG	Fasting plasma glucose
FSC	French Society of Cardiology
GLP-1RAs	Glucagon-like peptide-1 receptor agonist
GS	Glucose Solution
HbA1c	Glycated hemoglobin A1c
ICU	Intensive Care Unit
IV	Intravenous
KATP	Potassium adenosine triphosphate-dependent channels
LVEF	Left ventricular ejection fraction
MET	Metabolic equivalents
MI	Myocardial infarction
OGTT	Oral glucose tolerance test
Peak VO2	Peak oxygen uptake
TNF a	Tumor necrosis factor alpha

2. Methodology

This review article is based on a literature search over a period of 3 months, using Google Scholar, PubMed, ScienceDirect, and Springer Link as search engines. We combined the terms diabetes, hyperglycemia, oral antidiabetics, and insulin therapy to the terms acute coronary syndrome, intensive care unit, and myocardial infarction as either keywords or MeSH terms. The search was limited to English and French articles. The retrieved articles were reviewed for potentially relevant studies and reviews.

3. Pathophysiology

The stress state caused by myocardial ischemia leads to massive secretion of catecholamines, via the sympathetic system and adrenal glands, which increases blood glucose levels by stimulating hepatic glycogenolysis and gluconeogenesis, decreasing peripheral glucose use and insulin sensitivity. In addition, cytokines also play a major role in the response to stress. Tumor necrosis factor, interleukin-1 and interleukin-6 stimulate the hypothalamus–pituitary axis to produce corticotropin releasing hormone and adrenocorti-

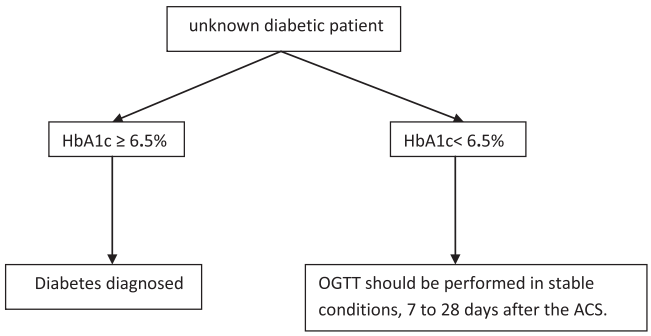

Figure 1. Screening algorithm for carbohydrate metabolism disorders in patients with ACS. ACS = acute coronary syndrome; HbA1c = glycated hemoglobin A1c; OGTT = oral glucose tolerance test.

cotropic hormone that act directly on the adrenal cortex to increase glucocorticoid synthesis, which also increases blood glucose level [3].

Under normal conditions, the coronary flow ensures a good supply of substrates and oxygen to the myocardium that preferentially metabolizes free fatty acids (70%) with a high energy yield (each molecule of fatty acid produces 130 molecules of adenosine triphosphate; ATP). In an ischemic state, myocardial metabolism shifts towards preferential anaerobic carbohydrate usage. However, the energy yield of this pathway is low since a molecule of glucose only produces two molecules of ATP against 38 in the presence of oxygen. To oppose this metabolic shift, the myocardium develops resistance to insulin, which may be another explanation for the hyperglycemia observed in ACS [4].

In cases of myocardial ischemia, the elevated plasma concentration of free fatty acids, particularly nonesterified fatty acids, due to catecholamine-induced lipolysis is deleterious. They increase the risk of cardiac arrhythmia, high blood pressure, and endothelial dysfunction [5]. Also, hyperglycemia increases the size of the infarct by causing myocardial cell death through apoptosis, and reducing collateral blood flow [6,7].

4. Screening for glucose metabolism abnormalities on admission for ACS

Stress hyperglycemia on admission after ACS is common and is a powerful predictive factor in survival and occurrence of complications, which justifies systematic blood glucose measuring at admission. However, this glucose level is not considered a diagnostic tool for diabetes or intermediate hyperglycemia in nondiabetic patients, but does lead to initiation of early treatment with continuous infusion of insulin if blood glucose is >180 mg/L [8,9].

According to the World Health Organization, screening for glucose metabolism profile should be based on the oral glucose tolerance test (OGTT) and fasting plasma glucose (FPG) [10]. Glycated hemoglobin A1c (HbA1c) allows us to assess glycemic profile. Diagnosis of diabetes is suggested if HbA1c is $\geq$6.5%, yet HbA1c <6.5% does not exclude the diagnosis and should prompt an OGTT in patients at high risk of carbohydrate metabolism disorders [1].

During stress, especially during the early phase of ACS, FPG has no place in the screening and classification of glucose tolerance [11], while OGTT is recommended for screening, provided it is done after patient stabilization (between 7 days and 28 days after ACS) [8,11]. This is because an OGTT carried out early during the acute phase of MI does not reliably reflect long-term metabolic profile [12]. Theoretically, HbA1c is interesting because it provides information about the carbohydrate metabolism profile in the last 2–3 months, therefore, the results are not influenced by stress. After ACS, HbA1c $\geq$6.5% has a positive predictive value of 100% for predicting an OGTT >2 g/L [13]. Thus, HbA1c can be used instead of OGTT for diagnosis of diabetes after ACS.

All patients admitted for ACS who are not known to have diabetes should undergo systematic screening for diabetes [9]. This screening can be done on admission by measuring HbA1c. If HbA1c is $\geq$6.5%, the patient may be considered to have diabetes, but HbA1c <6.5% does not exclude diagnosis of diabetes mellitus, and an OGTT should be performed after stabilization for complete evaluation of glucose metabolism (Fig. 1).

Table 1. Summary of selected randomized trials evaluating insulin infusion effect on major cardiovascular events in patients admitted for acute coronary syndrome.

Study	DIGAMI [16]	ECLA [46]	GIPS [47]	POL-GIK [17]	HI-5 [48]
No. of patients	620	407	940	954	240
Dose (U/h)	5	1.4/5.2	5	1.3 → 0.8	2
Insulin perfusion duration (h)	24–72	24	24	24	24
Glucose level target (g/dL)	1.26–1.80	1.26–1.98	1.26–1.98	<3	0.72–1.80
Results	↓Mortality	↓Mortality	↓Mortality	↑Mortality	↑Mortality

5. Management of hyperglycemia/ hypoglycemia in cardiac intensive care units

Several studies have determined target blood glucose levels. A randomized controlled trial performed in intensive care units (ICUs) of Leuven University Hospital, demonstrated that intensive insulin therapy (glycemia level 0.8–0.11 g/L in adults) reduced morbidity and mortality compared to conventional therapy (insulin administered when the blood glucose level exceeded 2,15 g/L, with the infusion tapered when the level fell below 1,80 g/L). [14]. However, The Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study [15], one of the largest international randomized trials, found that intensive glucose control increased mortality among adults in the ICU. A blood glucose target of 1.40–1.80 g/L resulted in lower mortality versus a target of 0.81–1.08 g/L (the mortality of the group with blood glucose target of 1.40–1.80 g/L 751/3012 vs. the mortalitry of the group with intensive glucose control 829/3010, $p = 0.02$) [15]. The above studies included patients in the ICU (with or without ACS). Other studies have addressed the question only in ACS patients (Table 1). They have shown that, regardless of the insulin therapy protocol used, control of blood sugar level to between 1.26 g/L and 1.80 g/L was associated with a significant reduction in mortality in the acute phase, and at 3 months, 1 year, and even at 3 years after ACS [16]. Stricter control for lower glycemic levels (<1.40 g/L) was associated with increased mortality and risk of hypoglycemia, which exposed the patients to seizures, brain damage, depression, and arrhythmias. If strict control is dangerous, hyperglycemia >2 g/L is also associated with a significant increase in mortality [17]. Based on the results of randomized studies, it seems reasonable to aim for glycemic levels between 1.40 g/L and 1.80 g/L. This agrees with the recommendations of the European Society of Cardiology that state that the treatment of hyperglycemia should avoid both excessive hyperglycemia (>1.80–2.0 g/L) and hypoglycemia (<0.90 g/L) during the acute phase of ACS [18].

Table 2. Initial dose of insulin therapy in intensive care unit according to glycemia at admission.

Admission blood glucose level	Insulin dose
1.80–3.0 g/L (10–16.6 mmol/L)	2 U/h
3.0–4.0 g/L (16.6–22.2 mmol/L)	3 U/h
>4 g/L (22.2 mmol/L)	4 U/h

Table 3. Insulin dose according to monitored blood glucose level during hospitalization in intensive care unit.

Blood glucose level	Insulin dose
<0.8 g/L (4.4 mmol/L)	Stop insulin
0.80–1.40 g/L (4.4–7.8 mmol/L)	Lowered by 0.5 U/h
1.40–1.80 g/L (7.8–10 mmol/L)	Unchanged
1.80–3.0 g/L (10.0–16.6 mmol/L)	Elevated by 1 U/h
>3 g/L (16.6 mmol/L)	Elevated by 1.5 U/h

Table 4. Particularity of patients older than 75 years.

Blood glucose level	Insulin dose
<0.8 g/L (4.4 mmol/L)	Stop insulin
0.80–1.40 g/L (4.4–7.8 mmol/L)	Stop insulin
1.40–1.80 g/L (7.8–10.0 mmol/L)	Unchanged
1.80–3.0 g/L (10.0–16.6 mmol/L)	Elevated by 0.5 U/h
>3 g/L (16.6 mmol/L)	Elevated by 1 U/h

Regarding the treatment protocol that could optimize blood glucose control, one study has compared 12 different insulin infusion protocols used in medical and surgical ICUs, but the results have not established the superiority of any of the protocols [19]. This explains the lack of consensus in this regard, but most scientific societies agree about the need for intravenous insulin therapy with concomitant infusion of glucose solution to target a blood glucose level of 1.40–1.80 g/L [8,18]. Glucose–insulin–potassium infusions were found to be of no value and potentially harmful in a combined analysis of two large randomized trials [18,20].

The lack of consensus has led the Diabetes and Cardiovascular Disease Study Group of the Francophone Diabetes Society, in cooperation with the French Society of Cardiology to propose a protocol of intravenous insulin therapy within the ICU.

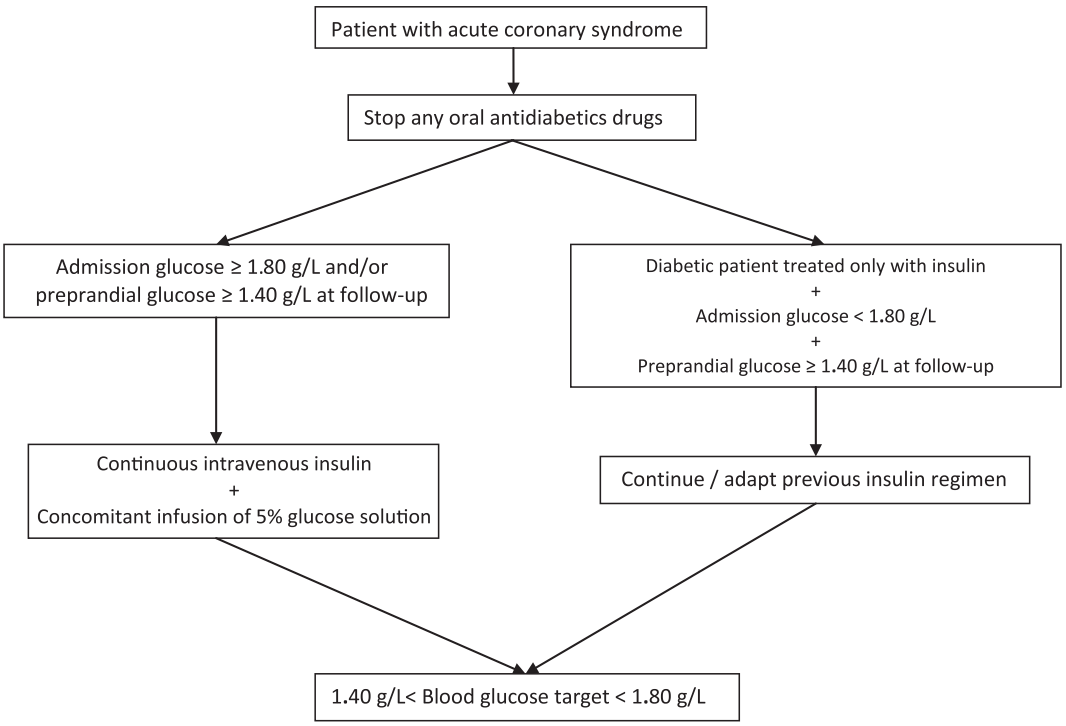

Figure 2. Management algorithm for hyperglycemia in cardiology intensive care units.

The protocol uses insulin analogs (50 U diluted in 50 mL 5% glucose solution) with concomitant infusion of 5% glucose solution so that the patient receives a total of 150 g/day carbohydrate. The initial dose of insulin therapy depends on blood glucose level at admission (Table 2). This dose is adjusted to the level of blood glucose monitored 1 hour after initiation, then every 2 hours (Table 3). In patients older than 75 years, the insulin dose can be adapted to blood glucose level as follows (due to the risk of hypoglycemia) (Table 4).

If the patient eats, a preprandial rapid insulin bolus of 4 U is administered subcutaneously. Thereafter, the dose of this bolus is adapted according to the postprandial glucose level. In cases of mild hypoglycemia (blood glucose <0.80 g/L), insulin infusion is stopped, followed by oral administration of 15 g sugar with glucose monitoring every 30 minutes. Insulin infusion is restarted when blood glucose is >1.40 g/L, at half the previous infusion rate. In cases of severe hypoglycemia (blood glucose <0.40 g/L), insulin infusion is stopped immediately, followed by intravenous administration of 30% glucose solution. In the following special case, if a known diabetic patient is treated with insulin and has an admission blood glucose <1.80 g/L and/or preprandial blood glucose <1.40 g/L during hospitalization in the ICU, the insulin regimen used before hospitalization can be continued. In these patients, blood glucose should be monitored before and 2 hours after each meal, and at bedtime (Fig. 2). All other antidiabetic treatment should be interrupted during hospitalization in the ICU. Whether the patient has diabetes or not, glucose level ≥1.80 g/dL should lead to intravenous insulin therapy as soon as the patient is admitted to the ICU (Fig. 2).

Management of hyperglycemia during hospitalization in the cardiology inpatient unit

After hospitalization in the ICU, insulin therapy is no longer recommended in all patients, and other therapeutic measures should be considered. It is recommended, depending on the metabolic profile and glycemic control of the patient, to switch to a fixed insulin regimen or an oral antidiabetic.

5.1. Oral antidiabetics

5.1.1. Metformin

Metformin is an insulin-sensitizing drug, belonging to the biguanide family, which reduces the level of glucose in the blood primarily by decreasing hepatic glucose production by inhibiting gluconeogenesis and hepatic glycogenolysis [21].

In ACS, scientific societies agree that metformin is not contraindicated during hospitalization in a post-ICU [8]. Regarding the risk of lactic acidosis associated with metformin use, a study published in the Cochrane Collaboration has demonstrated that there is no evidence from prospective comparative trials or observational cohort studies that, compared with other antidiabetic agents, metformin is associated with an increased risk of lactic acidosis or increased lactate level in the blood [22]. In the Reduction of Atherothrombosis for Continued Health (REACH) registry, a significant reduction in 2-year mortality was observed with metformin in patients with type 2 diabetes and a history of cardiovascular disease [adjusted hazard ratio: 0.76 (0.65–0.89); $p < 0.001$] [23]. Based on safety, tolerance, low risk of hypoglycemia, and low cost of the drug, as well as randomized clinical trials that have shown a reduction in cardiovascular mortality compared to that with other oral antidiabetics, metformin should be the first-line oral antidiabetic to be considered in type 2 diabetes, in the absence of contraindications and intolerance [24].

5.1.2. Sulfonylureas

The sulfonylureas are the oldest oral hypoglycemic drugs and have been used since 1950. They are insulin-secreting molecules that act by inhibiting potassium ATP-dependent channels (KATP channels) of pancreatic beta cells, which induces closure of these channels, and therefore, rapid cell depolarization and insulin secretion through Ca^{2+} cell penetration. Therefore, the blood glucose-lowering efficacy of these molecules depends on the residual capacity of the pancreas to secrete insulin.

However, the isoform units of the KATP channel are also found in blood vessels and myocardial cells whose activation causes initially a decrease in contractility of cardiomyocytes, then coronary vasodilatation that protects the myocardium from ischemia and reduces the extent of myocardial necrosis. This protective phenomenon is called ischemic preconditioning. Sulfonylureas, with relative specificity towards pancreatic beta cells, can inhibit this protective reaction [25].

In animal models of MI, it has been shown that activation of KATP channels reduces infarct size [26]. In humans, it has been observed that treating patients intensively with first-generation sulfonamides and glibenclamide is associated with a high mortality rate linked to MI [27,28]. This blocking effect could be a possible explanation. However, there has been no observed increase in mortality or congestive heart failure incidence in patients receiving sulfonamides selective for pancreatic cells, especially gliclazide and glimepiride [28].

Furthermore, sulfonylurea usage is associated with the risk of hypoglycemia, both severe and non-severe [29], which reduces well-being and quality of life by increasing anxiety and fear of repeated events, and exposes the patient to brain damage and arrhythmias [30,31].

For all these reasons, the first-generation sulfonamides and glibenclamide should not be used after ACS [8].

5.1.3. Gliflozins

The EMPA-REG OUTCOME study has shown that empagliflozin decreased significantly cardiovascular mortality (3.7% vs. 5.9% in the placebo group; 38% relative risk reduction) and hospitalization for heart failure (2.7% vs. 4.1% in the placebo group; 35% relative risk reduction), without impact on the incidence of myocardial infarction or stroke [32].

5.1.4. Incretin-based therapies

Glucagon-like peptide-1 receptor agonists are associated with a significant decrease in the risk of major cardiovascular events, when they are compared with placebo [33]. Their long-term cardiovascular safety and potential to prevent cardiovascular disease in type 2 diabetes patients with high cardiovascular risk appear promising, but remain uncertain in patients with a low cardiovascular risk [34]. In contrast, the ELIXA study showed that the addition of lixisenatide to usual care did not significantly alter the rate of major cardiovascular or other serious adverse events in patients with type 2 diabetes who had had an MI or had been hospitalized for unstable angina within the previous 180 days [35]. Thus the safety of glucagon-like peptide-1 receptor agonists in patients with high cardiovascular risk.

Cardiovascular safety of dipeptidyl peptidase- 4 inhibitors following ACS, particularly alogliptin, has been demonstrated since the large prospective study (EXAMINE) showing noninferiority versus placebo in terms of major adverse cardiovascular events in type 2 diabetic patients who presented with acute MI or unstable angina requiring hospitalization within the previous 15–90 days [36].

5.1.5. Other oral antidiabetics

For other oral antidiabetics, according to the Heart and Diabetes Study Group, the Francophone

Diabetes Society in collaboration with the French Society of Cardiology [8] recommend the following: glinides are not contraindicated after ACS; acarbose can be used after ACS when needed, depending on the patient's metabolic phenotype (predominant postprandial hyperglycemia); and pioglitazone is not contraindicated after ACS unless there is congestive heart failure or left ventricular ejection fraction <45%.

5.2. Fixed protocol of insulin

After transfer to the cardiology inpatient unit, continuous infusion of insulin must be stopped and switching to a subcutaneous insulin-based protocol should be considered. In this context, Avanzini et al. [37] have proposed a protocol that has proven its efficacy and safety in diabetic and nondiabetic patients with hyperglycemia and ACS, which consists of:

(1) calculating the number of insulin units infused during the last 12 hours to obtain the average hourly infused insulin and multiply by 24 to obtain the required daily dose of insulin; (2) dividing the 24-hour dose of insulin into two parts: the first to be administrated in the form of rapid-acting insulin analog, and the second as a long-acting insulin analog; (3) long-acting insulin analog administrated subcutaneously 2 hours before the first meal after stopping insulin infusion; (4) daily dose of insulin should be split into three: 20% at breakfast, 40% at lunch, and 40% at dinner.

6. Management of diabetes during the rehabilitation phase

During the rehabilitation phase, many studies have proved the benefits of physical activity on glycemic control. It is estimated that physical activity can reduce the rate of HbA1c by 0.6% compared to its initial value, and could therefore help reduce diabetic complications [38].

Regular physical exercise also improves glucose tolerance and lowers insulin resistance, thus delaying the onset of type 2 diabetes in patients with intermediate hyperglycemia [39]. In addition to its beneficial effect on weight reduction, exercise helps control blood pressure, promotes psychological well-being, and reduces the incidence of depression, which is common in diabetic patients with coronary artery disease, and improves quality scores as well as treatment adherence [40].

Peak exercise capacity (assessed as peak oxygen uptake; peak VO2) measured in metabolic equivalents is an important prognostic factor. A gain in VO2 peak after cardiac rehabilitation is associated with reduced mortality and morbidity [41,42]. The DARE study has demonstrated that, in type 2 diabetes, good glycemic control during cardiac rehabilitation following ACS is an independent factor associated with a gain in peak VO2 (3.5 ± 2.4 vs. 1.7 ± 2.4 mL/kg/min, $p = 0.014$) [43]. This emphasizes the need for good glycemic control during cardiac rehabilitation in type 2 diabetic patients.

Blood glucose should be monitored prior to exercise in all diabetic patients, at the end, and 4–6 hours after the exercise session in patients treated with insulin. If blood sugar prior to exercise is >2.5 g/L, ketonuria should be investigated, if it is negative and the patient is properly hydrated, exercise can be performed with caution (control of capillary glycemia must be performed every hour during the session) [8].

7. When should a diabetic patient be referred to a diabetologist?

Hospitalization for an ACS is an opportunity to optimize diabetes treatment and patient education [44]. Furthermore, it has been shown that involving a diabetologist in the management of patients hospitalized for conditions other than diabetes could reduce significantly the average hospitalization duration of 8.2 days to 5.5 days [45].

During hospitalization in the ICU, treatment of hyperglycemia in patients requiring insulin therapy should be delivered by an experienced team, including a diabetologist [8].

Before hospital discharge, transfer to a diabetes/endocrinology service is indicated in cases of unknown diabetes with HbA1c $\geq$6.5%, in cases of poorly controlled diabetes with HbA1c $\geq$8%, if insulin therapy is newly introduced, or if serious and/or repeated hypoglycemia occurs [8].

Throughout the rehabilitation phase, a diabetologist should be involved if diabetes is uncontrolled with significant hyperglycemia or in the case of serious or repeated hypoglycemia [8].

8. Conclusion

Given the frequency and poor prognosis of hyperglycemia during ACS, clear management recommendations are necessary. The data published so far have shown that overly strict glycemic targets should be banned. The use of continuous infusion of IV insulin is recommended during hospitalization in an ICU if admission

blood glucose exceeds 1.8 g/L, with a target between 1.4 g/L and 1.8 g/L. Close collaboration between diabetologists and cardiologists is crucial to better management of these patients.

References

[1] Rydén L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, et al.. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2013;34:3035–87.
[2] Karetnikova V, Gruzdeva O, Uchasova E, Osokina A, Barbarash O. Glucose levels as a prognostic marker in patients with ST-segment elevation myocardial infarction: a case–control study. BMC Endocr Disord 2016;16:31.
[3] Mizock BA. Blood glucose management during critical illness. Rev Endocr Metab Disord 2003;4:187–94.
[4] McGuire DK. Diabetes and the cardiovascular system. In: Mann DL, Zipes DP, Libby P, Bonow RO, editors. Braunwald's heart disease: a textbook of cardiovascular medicine. New York: Elsevier Saunders; 2014. p. 1365–90.
[5] Clement S, Braithwaite SS, Magee MF, Ahmann A, Smith EP, Schafer RG, et al.. Management of diabetes and hyperglycemia in hospitals. Diabetes Care 2004;27:553–91.
[6] Kersten JR, Toller WG, Tessmer JP, Pagel PS, Warltier DC. Hyperglycemia reduces coronary collateral blood flow through a nitric oxide-mediated mechanism. Am J Physiol Heart Circ Physiol 2001;281:H2097–104.
[7] Ceriello A, Quagliaro L, D'Amico M, Di Filippo C, Marfella R, Nappo F, et al.. Acute hyperglycemia induces nitrotyrosine formation and apoptosis in perfused heart from rat. Diabetes 2002;51:1076–82.
[8] 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;38:113–27.
[9] Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, et al.. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2016;37:267–315.
[10] World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Geneva: World Health Organization; 1999.
[11] Paulweber B, Valensi P, Lindström J, Lalic NM, Greaves CJ, Mckee M, et al.. A European evidence-based guideline for the prevention of type 2 diabetes. Horm Metab Res 2010;42(Suppl 1):S3–S36.
[12] Knudsen EC, Seljeflot I, Abdelnoor M, Eritsland J, Mangschau A, Arnesen H, et al.. Abnormal glucose regulation in patients with acute ST- elevation myocardial infarction-a cohort study on 224 patients. Cardiovasc Diabetol 2009;8:6.
[13] Ishihara M, Inoue I, Kawagoe T, Shimatani Y, Kurisu S, Hata T, et al.. Is admission hyperglycaemia in non-diabetic patients with acute myocardial infarction a surrogate for previously undiagnosed abnormal glucose tolerance? Eur Heart J 2006;27:2413–9.
[14] 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;354:449–61.
[15] NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283–97.
[16] Malmberg K, Ryden L, Efendic S, Herlitz J, Nico P, Waldenstrom 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;26:57–65.
[17] Ceremuzynski L, Budaj A, Czepiel A, Burzykowski T, Achremczyk P, Śmielak-Korombel W, et al.. Low-dose glucose-insulin-potassium is ineffective in acute myocardial infarction: results of a randomized multicenter Pol-GIK trial. Cardiovasc Drugs Ther 1999;13:191–200.
[18] Steg PG, James SK, Atar D, Badano LP, Bldmstrom-Lundqvist C, Borger MA, et al.. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33:2569–619.
[19] Wilson M, Weinreb J, Hoo GW. Intensive insulin therapy in critical care: a review of 12 protocols. Diabetes Care 2007;30:1005–11.
[20] 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;298:2399–405.
[21] Inzucchi SE, McGuire DK. New drugs for the treatment of diabetes: part II: incretin-based therapy and beyond. Circulation 2008;117:574–84.
[22] Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus (Review). Cochrane Database Syst Rev 2010(4) CD002967.
[23] Roussel R, Travert F, Pasquet B, Wilson PWF, Smith SC, Goto S, et al.. Metformin use and mortality among patients with diabetes and atherothrombosis. Arch Intern Med 2010;170:1892–9.
[24] American Diabetes Association. Standards of medical care in diabetes – 2013. Diabetes Care 2013;36(Suppl 1):S11–66.
[25] Brad PA, Terzic A. The sulfonylurea controversy: more questions from the heart. J Am Coll Cardiol 1998;31:950–6.
[26] Maruyama I, Tomiyama Y, Maruyama K, Ojima K, Kobayashi K, Kobayashi M, et al.. Effects of mitiglinide and sulfonylureas in isolated canine coronary arteries and perfused rat hearts. Eur J Pharmacol 2006;531:194–200.
[27] Garratt KN, Brady PA, Hassinger NL, Grill DE, Terzic A, Holmes DR, et al.. Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. J Am Coll Cardiol 1999;33:119–24.
[28] Zeller M, Danchin N, Simon D, Vahanian A, Lorgis L, Cottin Y, et al.. Impact of type of preadmission sulfonylureas on mortality and cardiovascular outcomes in diabetic patients with acute myocardial infarction. J Clin Endocrinol Metab 2010;95:4993–5002.
[29] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al.. Management of hyperglycemia in type 2 diabetes: a patient-centred approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364–79.
[30] Harris S, Mamdani M, Galbo-Jørgensen CB, Bøgelund M, Gundgaard J, BPharm DG, et al.. The effect of hypoglycemia on health-related quality of life: Canadian results from a multinational time trade-of survey. Can J Diabetes 2014;38:45–52.
[31] Marques JL, George E, Peacey SR, Harris ND, Macdonald IA, Cochrane T, et al.. Altered ventricular repolarization during hypoglycaemia in patients with diabetes. Diabet Med 1997;14:648–54.
[32] Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al.. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–28.
[33] Monami M, Cremasco F, Lamanna C, Colombi C, Desideri CM, Iacomelli I, et al.. Glucagon-like peptide-1 receptor agonists and cardiovascular events: a meta-analysis of randomized clinical trials. Exp Diabetes Res 2011;2011:215764.
[34] Dalsgaard NB, Brønden A, Vilsbøll T, Knop FK. Cardiovascular safety and benefits of GLP-1 receptor agonists. Expert Opin Drug Saf 2017;16:351–63.

[35] Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, et al.. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015;373:2247–57.
[36] White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, et al.. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013;369:1327–35.
[37] Avanzini F, Marelli G, Donzelli W, Busi G, Carbone S, Bellato L, et al.. Desio Diabetes Diagram Study Group. Transition from intravenous to subcutaneous insulin: effectiveness and safety of a standardized protocol and predictors of outcome in patients with acute coronary syndrome. Diabetes Care 2011;34:1445–50.
[38] Thomas DE, Elliott EJ, Naughton GA. Exercise for type 2 diabetes mellitus. Cochrane Database Syst Rev 2006;19(3): CD002968.
[39] Laaksonen DE, Lindstrom J, Lakka TA, Eriksson JG, Niskanen L, Wikström K, et al.. Physical activity in the prevention of type 2 diabetes: the Finnish diabetes prevention study 1. Diabetes 2005;54:158–65.
[40] Milani RV, Lavie CJ. Behavioral differences and effects of cardiac rehabilitation in diabetic patients following cardiac events. Am J Med 1996;100:517–23.
[41] Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 2002;346:793–801.
[42] Kavanagh T, Mertens DJ, Hamm LF, Beyene J, Kennedy J, Corey P, et al.. Prediction of long-term prognosis in 12 169 men referred for cardiac rehabilitation. Circulation 2002;106:666–71.
[43] Vergès B, Patois-Vergès B. Iliou M-C, and DARE Study group. Influence of glycemic control on gain in VO2 peak, in patients with type 2 diabetes enrolled in cardiac rehabilitation after an acute coronary syndrome. The prospective DARE study. BMC Cardiovasc Disord 2015;15:64.
[44] Levetan CS, Passaro M, Jablonski K, Kass M, Ratner RE. Unrecognized diabetes among hospitalized patients. Diabetes Care 1998;21:246–9.
[45] Levetan CS, Salas JR, Wilets B, Zumoff B. Impact of endocrine and diabetes team consultation on hospital length of stay for patients with diabetes. Am J Med 1995;99:22–8.
[46] Diaz R, Paolasso EA, Piegas LS, Tajer CD, Moreno MG, Corvalán R. Metabolic modulation of acute myocardial infarction. The ECLA (Estudios Cardiologicos Latinoamerica) Collaborative Group. Circulation 1998;98:2227–34.
[47] van der Horst IC, Zijlstra F, van't Hof AW, Doggenet CJM, de Boer M-J, Suryapranata H. Glucose-insulin-potassium infusion in patients treated with primary angioplasty for acute myocardial infarction: the glucose-insulin-potassium study: a randomized trial. J Am Coll Cardiol 2003;42:784–91.
[48] Cheung NW, Wong VW, Mc Lean 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;29:765–70.