Chapter 4

# Coronary Artery Bypass Grafting in Patients with Diabetes Mellitus: A Cardiologist's View

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http://dx.doi.org/10.5772/intechopen.70416

**Abstract**

The review presents current data on the prevalence of diabetes in the cohort of patients undergoing coronary artery bypass grafting. The relevance of active approach to the identification of diabetes and prediabetes in patients with coronary artery disease (CAD) before coronary revascularization is reviewed. Recent information about the negative impact of diabetes on the prognosis of myocardial revascularization is reported as well as the main mechanisms responsible to the development of adverse outcomes of interventions in these patients. Target perioperative values of glycemia recommended by the leading associations of the study of diabetes have been compared. Beneficial potential of other carbohydrate metabolism markers (glycated hemoglobin, fructosamine, 1,5-anhydroglucitol) in patients with diabetes mellitus (DM) in terms of their impact on cardiovascular prognosis, including coronary intervention. The results of studies comparing different management strategies for these patients are reviewed. The significance of carbohydrate metabolism compensation during myocardial revascularization is reported; thus, a too stringent glycemic control has no benefits neither for percutaneous nor for open coronary intervention. Recent trials suggest the groups of antidiabetic drugs and evidence of their impact on the cardiovascular system. The importance of comprehensive monitoring of major risk factors in diabetic patients with coronary intervention has been proved.

**Keywords:** diabetes mellitus, prediabetes, early diagnosis of diabetes, ischemic heart disease, coronary artery bypass surgery, percutaneous coronary intervention, myocardial revascularization, target levels of glycemic control, glycated hemoglobin, perioperative antihyperglycemic therapy, perioperative management

## 1. Introduction

Diabetes mellitus (DM) is one of the most common comorbid conditions in patients with coronary artery disease (CAD), which is important in determining the severity of the disease, treatment strategy, and the prognosis of patients [1].

The increasing prevalence of diabetes has led to a situation where over 380 million people had diabetes mellitus globally in 2013, of whom 99% suffered from type 2 diabetes [2]. According to the population statistics, the number of people present with diabetes is increasing annually. By 2030, this number is expected to rise to more than 550 million people with diabetes and up to 300 million people with prediabetes [2]. This dramatic rise is fuelled mainly by the aging of the population and continuing changes in eating habits and lifestyle with predominant sedentary behavior. In 2014, an estimated 4.9 million deaths were caused by diabetes, of which 60% had the underlying cardiovascular diseases (CVDs) [2].

Therefore, teamwork of cardiologists and endocrinologists is needed to optimally manage diabetes. The efforts of cardiology and diabetes communities have been recently targeted at developing joint guidelines and statements on diabetes management. All current guidelines on management of patients with stable and acute CAD, including guidelines on myocardial revascularization, contain a separate section on diabetes mellitus [3–6], whereas, the guidelines of the International Diabetes Federation, Canadian and American Diabetes Association devote separate sections on cardiovascular diseases (CVD) [7–10]. In 2013, the European Society of Cardiology developed the guidelines on diabetes, prediabetes, and cardiovascular diseases in collaboration with the European Association for the Study of Diabetes [11]. According to the updated guidelines, the search for approaches to optimize the negative impact of diabetes on the results of surgical management remains relevant and includes the study of optimal targets for carbohydrate metabolism, the improvements in the preoperative and perioperative management strategies [7–10]. This review covers the known and insufficiently studied issues of treating patients with diabetes mellitus undergoing myocardial revascularization from the perspective of evidence-based medicine.

## 2. Prevalence of diabetes in coronary revascularization

The management of CAD patients with concomitant diabetes who need myocardial revascularization is a great challenge. Recent studies demonstrated that a large proportion of CAD patients are present with diabetes [12–15]. The prevalence of diabetes among patients who have undergone percutaneous coronary intervention (PCI) varies greatly from 25 to 30%, according to the DES LATE, ISAR SAFE, RESET, SECURITY trials up to 35–39% in the EXCELLENT, OPTIMIZE, ITALIC, ARCTIC-Interruption trials, and CathPCI Registry [12–14]. The proportion of diabetic patients suffering from CAD undergoing coronary artery bypass grafting accounts for 22–48% of cases [16–20]. In a large Swedish Registry, comprising of 39,235 patients undergoing isolated CABG, 22.8% of patients had diabetes mellitus [18]. The prevalence of diabetes among patients undergoing coronary artery bypass grafting (CABG) is 20–23% according to the results of the Russian studies [20, 21], whereas the US CABG registry suggested the diabetes prevalence to be of 46.9% [19]. A recent Japanese study reported that the proportion of patients with diabetes undergoing direct myocardial revascularization reaches 48% [16].

Differences in diabetes prevalence rates are mainly caused by different diagnostic approaches and racial/ethnic disparities. A large-scale multi-ethnic registry study CREDO-Kyoto comprised 15,580 patients undergoing either CABG or PCI [29]. The lowest rate of diabetes was found in the Caucasian group, whereas the highest ones in the African Americans and the Hispanic group (26.9 vs. 44 vs. 49.5%, respectively). The prevalence rate in the Japanese group was 39% [29].

In addition, several studies confirmed a steady increase in the proportion of diabetic patients undergoing coronary revascularization. In the period from 1999 to 2008, in the Chinese cohort of patients who have undergone CABG, the proportion of diabetic patients increased from 20 to 32% [17], whereas in the American—from 26 to 46% [19]. Moreover, a recent study demonstrated that the rate of diabetes increased by 32% among the patients undergoing CABG [22].

## 3. Early diagnosis of diabetes in CAD patients undergoing myocardial revascularization

The sharp increase in the prevalence of diabetes among interventional cardiology and cardiac surgery patients is caused by the aging of the population, expanding clinical indications for myocardial revascularization, and recent advances in diagnostic strategies for diabetes and other glycemic disorders [11]. The leading medical associations and communities use the same cut-offs to establish the diagnosis of diabetes mellitus: a fasting plasma glucose concentration ≥ 7.0 and/or 11.1 mmol/l after postglucose load and meal, and/or glycated hemoglobin (HbA1c) >6.5% [7, 8, 10]. However, there are some differences in diagnostic criteria for prediabetes based on fasting glucose and HbA1c. According to the American Diabetes Association (ADA), prediabetes is diagnosed if one or more of the following criteria are met: glycemia of 5.6 mmol/l or HbA1c of 5.7%; whereas the World Health Organization (WHO) implements the following criteria: glucose level of 6.1 mmol/l, or glycated hemoglobin of 6.0% [7, 10].

More rigorous approaches to the diagnosis of carbohydrate metabolism disorders are evident. Type 2 diabetes develops after a long period of euglycemia, but with the existing insulin resistance, which gradually turns into a deficit of beta cells with severe hyperglycemia. The development of CVD in individuals with insulin resistance is a long progressive process. When patients develop hyperglycemia and diagnose type 2 diabetes, 60% of them already have CVD [11, 23, 24].

The guidelines of the American Diabetes Association recommend to assess the glycemic state in adults of any age who are overweight or obese and who have one or more additional risk factors for diabetes (including cardiovascular diseases) and in all people aged >45 years [10]. The European Society of Cardiology and the European Association for the Study of Diabetes recommend if HbA1c and/or fasting plasma glucose (FPG) are inconclusive in individuals with CAD, no diabetes risk score is needed, but an oral glucose tolerance test (OGTT) is indicated [11]. Thus, all patients without previously diagnosed diabetes referred to elective coronary artery bypass grafting should be screened for diabetes or prediabetes.

The rationale for detecting disorders of carbohydrate metabolism has been demonstrated in several studies in patients with CAD, including those undergoing myocardial revascularization. Over 50% of myocardial infarction (MI) patients without known disorders of carbohydrate metabolism had positive OGTT in the in-hospital period [25].

The Spanish trial reported a high prevalence of diabetes up to 45% in patients undergoing PCI, based on continuous OGTT and glycated hemoglobin measurement. Importantly, a third of patients with positive testing were patients who had newly detected diabetes [26]. In their series, 28.8% had known diabetes, 16.2% newly detected diabetes, 25.5% prediabetes, and 29.5% were normoglycemics [26].

Balakrishnan et al. reported 39% of patients with diabetes out of 740 patients admitted to the hospital for PCI. Periprocedural measurement of glycated hemoglobin in patients without known disorders of glucose metabolism allowed to diagnose diabetes and prediabetes in 8.3 and 58.5% of patients, respectively [27].

A prospective Swedish study assessing the prevalence and prognostic impact of the different states of abnormal glucose regulation (AGR) after CABG reported the prevalence of known diabetes of 29.5% [28]. Out of the rest, 11.4% of patients had newly diagnosed diabetes based on oral glucose tolerance test. Thus, the proportion of patients with diabetes increased up to 41%. Another 24% of patients had prediabetes according to the postglucose load. A total of 65% of patients had disorders of carbohydrate metabolism [28].

Why do physicians need to perform active screening for undiagnosed diabetes in patients undergoing cardiac surgeries, and is there any rationale for it? Undiagnosed diabetes may affect the prognosis in this group of patients, similarly to previously diagnosed diabetes [25, 28, 29].

In the EARLY ACS trial of 8795 patients with non-ST-segment elevation ACS, newly diagnosed diabetes was a predictor of 30-day mortality or myocardial infarction [odds ratio (OR) 1.65; confidence interval (CI) 95%; 1.09–2.48] [29]. Previously diagnosed diabetes correlated with a 30-day mortality rate, but not with the MI rate [29].

Similarly, to known disorders of carbohydrate metabolism, newly diagnosed disorders affect the in-hospital and long-term prognosis of patients with myocardial infarction [25]. There was a successive increase in the risk of unfavorable cardiovascular events in the long-term period from normoglycemia through prediabetes to diabetes [28].

## 4. Benefits of coronary artery bypass grafting over percutaneous coronary intervention and medical therapy in diabetic patients with multivessel coronary artery disease

A sufficient number of studies aimed at choosing an optimal method for myocardial revascularization in patients with diabetes have been performed [30–37]. A large BARI-2D trial focused at assessing myocardial revascularization in patients with diabetes with stable coronary artery disease [30, 31]. Patients selected for the CABG stratum had more extensive coronary artery disease. Nevertheless, the rate of major cardiovascular events was significantly lower in the revascularization group, compared with the medical therapy group [30, 31].

The revascularization group patients demonstrated fewer cases of angina progression (8 vs. 13%, respectively, $p < 0.001$), recurrent angina (37 vs. 51%, respectively, $p < 0.001$), and subsequent coronary revascularization, compared to the intensive medical management group (18 vs. 33%, respectively, $p < 0.001$) [31]. The revascularization group patients exhibited a trend toward being angina-free at 3-year follow-up than the intensive medical management group (66 vs. 58%, respectively, $p < 0.003$). The superiority of revascularization strategy over medical therapy is believed to be caused by preferring CABG over PCI in patients with more severe coronary artery disease [31].

The FREEDOM (future revascularization evaluation in patients with diabetes mellitus) study is a single, well-powered, randomized trial, comparing CABG and PCI with first-generation drug-eluting stent (DES) (94%) in diabetic patients undergoing elective revascularization for multivessel coronary disease without left main coronary artery stenosis [33]. The rate of the primary outcome was lower in the CABG group than in the PCI group, with divergence of the curves starting at 2 years. This difference was due to a relative reduction in death from any cause ($p = 0.049$) and a significantly lower incidence of MI in the CABG group ($p < 0.001$) [33].

A review of 13 RCTs and 5 meta-analyses agreed that CABG surgery should be recommended in patients with diabetes and multivessel CAD, regardless of the severity of coronary anatomy: CABG improved the long-term prognosis. Thus, the 5-year risk of major cardiovascular events was 18.7% in the CABG group vs. 26.6% in the PCI group, $p = 0.005$) [34].

A recent meta-analysis of six RCTs showed similar results, confirming the benefits of direct revascularization over PCI in patients with diabetes. CABG was associated with a significantly lower mortality, compared with PCI (RR: 0.59, 95% CI 0.42–0.85; $p = 0.004$). The rates of major cardiovascular and cerebrovascular events, as well as repeat revascularization, were significantly lower in the CABG group (OR 0.51, 95% CI 0.27–0.99, $p = 0.03$ vs. OR 0.34, 95% CI 0.24–0.49; $p < 0.00001$, respectively) [35].

Since available data suggesting beneficial effects of myocardial revascularization in patients with diabetes were obtained in the period of advancements in pharmacotherapy and technology of both PCI and surgical revascularization, it is difficult to compare them directly. Nevertheless, many studies have shown that CABG appears to be a better option compared to PCI with DES in diabetic patients, particularly, if the patient has multivessel CAD [33–37]. The superiority of coronary artery bypass grafting over percutaneous coronary intervention in diabetic patients with multivessel coronary disease is currently stated in the international guidelines with the class of recommendation IA [5].

## 5. Diabetes mellitus and outcomes of myocardial revascularization

Although diabetic patients constitute an increasing number of individuals undergoing PCI and surgical revascularization, they have worse outcomes, than non-diabetic patients [14, 37–39]. The meta-analysis of several randomized clinical trials of coronary angioplasty using bare-metal stents has proved diabetes to be the strongest predictor of restenosis, with a high risk of repeat revascularization of the target lesion [37]. In multivariable analyses of 6081 patients undergoing PCI with the implantation of DES, diabetic vs. non-diabetic patients had higher risks of major adverse cardiac events (odds ratio (OR), 1.25; 95% confidence interval (CI), 1.03–1.53; $p = 0.026$), but similar risks of cardiac death (OR, 1.41; 95% CI, 0.96–2.07; $p = 0.08$) and myocardial infarction (OR, 0.89; 95% CI, 0.64–1.22; $p = 0.45$) [38].

The two major causes of stent failure are stent thrombosis and in-stent restenosis. The incidence of both has reduced considerably in recent years [14]. Current clinical registries and randomized trials with broad inclusion criteria show rates of stent thrombosis at or <1% after 1 year; rates of clinical in-stent restenosis are 5%, respectively [12–14]. Angiographic surveillance studies in large cohorts show rates of angiographic in-stent restenosis of ~10% with new-generation DES [14]. However, the contribution of diabetes to the development of restenosis remains significant. One of the largest analysis, comprising of 10,004 patients with completed angiographic follow-up after PCI found that diabetes mellitus was an independent predictor of restenosis (OR 1.32, 95% CI 1.19–1.46), as well as previous CABG, complex lesion morphology, smaller vessel reference diameter before the procedure, and greater stented length of the vessel [14]. Angiographic follow-up of 123 patients after PCI demonstrated that DM was associated with a 3-fold increased risk of plaque neovascularization. Importantly, more than half of the patients (56.5%) failed to reach the target range of glycated hemoglobin [40].

There is a strong association between diabetes and high rates of complications after CABG. Despite the fact that in-hospital mortality rates among diabetic patients significantly decreased from 3% in the period 1998–2002 to 1.3% in the period 2003–2005 [35], postoperative complication rates remain high. Thus, a retrospective analysis, comprising 667 CAD patients, who have undergone CABG, showed that diabetes did not affect in-hospital mortality, but was an independent predictor of sternal wound infection [41]. Similar findings were obtained in another retrospective study, suggesting the absence of any correlations between diabetes and the risk of cardiovascular complications and mortality. However, the obtained findings revealed a significant association between diabetes and renal complication after CABG [42]. Diabetic patients have poor immediate outcomes after CABG and unfavorable long-term prognosis, compared to non-diabetic patients. Moreover, patients with diabetes had higher rates of the hospitalization and major cardiovascular events [18, 28, 43]. A recent Russian study with the 5-year follow-up period reported that 14.2% of patients with diabetes had one of the major cardiovascular events (myocardial infarction, stroke, or cardiovascular death) vs. 6.3% patients without diabetes ($p = 0.028$) [39]. Despite new insights into pathophysiology of diabetes and recent improvements in the perioperative management, DM remains a challenging issue for coronary procedures and interventions.

## 6. Diabetes-specific risk factors for adverse prognosis in coronary procedures and interventions

Adverse prognosis in this group of patients is partially explained by initial characteristics of diabetic patients referred to elective revascularization. These patients commonly have higher perioperative risk due to advanced age, obesity, female gender, previous cardiovascular events and revascularization procedures, multivessel coronary disease, severe heart failure, chronic kidney disease, and chronic obstructive pulmonary disease. These conditions are known to independently affect the prognosis of patients with CAD [5, 23]. In addition, diabetic patients are more likely to have multivessel coronary disease, diffuse coronary lesions, poor distal vascular bed, and calcification [5].

However, there are diabetes-specific factors, namely hyperglycemia, insulin resistance, and hyperinsulinemia, which cause a cascade of pathogenetic reactions [44]. Thus, diabetic patients have more intense intravascular inflammation than non-diabetic ones. Excess pro-inflammatory cytokines and other biologically active substances lead to the destabilization of an atherosclerotic plaque, the progression of coronary atherosclerosis to unaffected segments of the vascular wall [44, 45]. Moreover, the analysis reported a diminished numerical density of mast cells and a significantly higher volume density of the mononuclear cells [46]. Hyperglycemia can lead to the development of endothelial dysfunction, associated with reduced nitric oxide, a key signaling regulator of vascular tone, and increased oxidative stress. In addition, acute hyperglycemia worsens insulin activity in endothelial cells even at physiologically adequate levels [23].

A prospective study, comprising of 1035 patients with myocardial infarction, who have undergone primary PCI in one of the Chinese hospitals, found a relationship between acute hyperglycemia at the time of admission and poor short- and long-term prognosis [47]. Pre- and postoperative hyperglycemia is the main risk factor for developing infectious complications after CABG in both diabetic and non-diabetic patients [41]. Hyperglycemia is associated with impaired leukocyte function, including diminished chemotaxis, decreased phagocytosis, impaired bacterial killing, and abnormal adhesive properties [44]. Diabetic patients showed higher endothelial activation and lower antiinflammatory response to CPB compared to non-diabetics [46]. Chronic hyperglycemia can lead to the central nervous system injury, resulting in diabetic encephalopathy with the onset of mild and moderate cognitive disorders [48]. Bruce et al. found that 64% of diabetic patients with coronary artery disease had cognitive or emotional disorders [49].

In addition, diabetes mellitus is a predictor of increased aggregation potential. SP-selectin, intercellular adhesion molecules, and platelet aggregation were significantly higher in diabetic patients, than in non-diabetics [44]. Despite receiving the same dose of aspirin and clopidogrel, patients with diabetes had higher values of platelet reactivity according to the findings of the recent study evaluating the effects of double antiplatelet therapy in diabetic patients with stable coronary artery disease [46]. Periprocedural control of glycemia in patients undergoing coronary interventions is pivotal for both endocrinologists and cardiologists. The current guidelines of the Canadian Diabetes Association (CDA) state that patients with diabetes do not receive the necessary glycemic control when they are admitted to non-profile hospitals [8].

## 7. Perioperative target glycemic range for myocardial revascularization and the risk of hypoglycemia

The current national guidelines, based on evidence-based medicine, have regulated the perioperative target range of glycemia [7–10]. The target range of glycemia for the majority of ICU patients, defined by the International Diabetes Federation, the American and Canadian Diabetes Associations, are the following: 140–180 mg/dL without hypoglycemia and 80–180 mg/dL for the perioperative period [8, 10].

All guidelines strictly recommend to avoid hypoglycemia. The risk of developing hypoglycemia inevitably increases with the attempts to achieve compensation for carbohydrate metabolism. Therefore, many studies, suggesting beneficial effects of perioperative glucose control, did not confirm their hypothesis [50–53]. A tighter control did not show its superiority neither for the immediate outcomes after CABG [50, 51], nor for the long-term outcomes [52]. Intensive insulin therapy with the achievement of perioperative target glucose levels of 100–140 (5.5–7.7 mmol/l) after CABG does not significantly reduce the number of postoperative complications, compared with the target glucose level of 140–170 (7.8–9.2 mmol/l) [51, 53].

A scientific statement from the American Diabetes Association and the American Heart Association Society suggests that severe hypoglycemia is the most likely cause of increased cardiovascular mortality in diabetic patients with intensive control of glycemia [54]. Unfortunately, hypoglycemia is more likely to happen when blood glucose decrease up to physiological values.

Hypoglycemia commonly develops with intensive insulin therapy, and is a well-known risk factor for MI, stroke, and death from any causes [53]. The relative risk for developing MI, associated with severe hypoglycemia 1 year before the index event, was 12%, 5.5 months before MI—20%, and 2 weeks before—65% [55].

Hypoglycemia triggers a powerful stimulation of the autonomic nervous system and the excess release of catecholamines, which promote vasospasm, tachycardia, arterial hypertension, and increased blood viscosity and coagulation [56]. These processes may cause changes in the regional blood flow and provoke myocardial or cerebral ischemia, resulting in myocardial infarction, heart failure, or stroke. Unfortunately, similar to fatal events, it is very difficult to demonstrate any relationship between severe hypoglycemia and serious vascular events, since clinical evidence of the impact of hypoglycemia are mainly random [55]. Death caused by hypoglycemia can be mistaken for death from acute coronary syndrome, because no one measures glycemia before. There are no anatomical and morphological postmortem signs of hypoglycemia [55, 56].

Withholding glucose in the target range without hypoglycemia and its impact on the prognosis are highly relevant issues for further research, as well as the use of integrated glucose metabolism indicators, such as glycated hemoglobin, which may improve the comprehensive risk assessment of surgical intervention.

## 8. Glycated hemoglobin and outcomes of coronary procedures and interventions

Glycated hemoglobin (HbA1c) is used for monitoring blood glucose levels in diabetic patients; it should be measured in all diabetic patients once in 3 months, and before any surgical interventions, including coronary revascularization. A systematic review of 11 studies addressing the relationship between glycated hemoglobin levels and the results of CABG in diabetic and non-diabetic patients was performed [57]. Four studies found significant increase in early and late mortality at higher HbA1c levels, regardless of a preoperative diagnosis of diabetes. In particular, the mortality risk for CABG is quadrupled at HbA1c levels >8.6% [57]. However, four studies of early mortality outcomes in diabetic patients only showed no significant differences between patients with normal and those with deranged HbA1c levels ($p = 0.99$). Three studies identified a significant increase in infectious complications in patients with poorly controlled HbA1c: superficial sternal wound infection ($p = 0.014$ and 0.007, respectively) and minor infections ($p = 0.006$) [57].

Unexpected data were obtained in one of the Japanese surgical clinics. Elevated HbA1c was associated with a lower incidence of arrhythmias after CABG. The incidence of postoperative atrial fibrillation was 28.3% in the lower tertile, 17.4% in the middle tertile, and 12.5% in the upper tertile [58]. Thus, the mean and high levels of glycated hemoglobin were associated with a lower incidence of atrial arrhythmias. One possible explanation is that patients with elevated HbA1c require more insulin, which has been reported to reduce the risk of postoperative atrial fibrillation [58]. Similar results were obtained in the recent American study. The incidence of atrial fibrillation after CABG was 20.9% in patients with HbA1c < 7.0% and 15.1% in patients with HbA1c ≥ 7.0% ($p = 0.007$), adjusted OR 0.73; 95% CI 0.55–0.96 [57]. However, elevated HbA1c was associated with higher rates of postoperative stroke, renal failure, and deep wound infection [57].

Some studies have called into question the predictive potential of HbA1c for short-term outcomes in well-controlled diabetics. However, poor control and elevated HbA1c may result in high rate of adverse events in the short- and long-term postoperative periods [57, 59].

Maintaining a level of glycemia close to the physiological level is an achievable goal of hypoglycemic therapy in type 2 diabetes. Its significance is evident and is associated with the risk of developing specific chronic complications induced by hyperglycemia. However, appropriate glycemic control with glucose levels closer to normal is associated with a high risk of hypoglycemia, which is known to affect the prognosis in diabetic patients with CVD [56]. Therefore, the search and development of optimal and safe tools to manage high glucose levels are pivotal for modern medical research.

## 9. The degree of compensation of carbohydrate metabolism and long-term prognosis in patients with diabetes and coronary artery disease

The UKPDS study was the first one to demonstrate the significance of the compensation of carbohydrate metabolism for the progression of complications [60]. The obtained results stimulated other researches in this area addressed to the assessment of the control intensity in patients with CVD, but the obtained data did not show the superiority of the tight strategy [61–63].

Three major studies (ACCORD, ADVANCE, and VADT) evaluated the impact of attaining euglycemia (ACCORD) or near-euglycemia (ADVANCE, VADT) in older patients with diabetes and high cardiovascular risk [61–63]. None of these studies, either individually or on pooled analysis, demonstrated any reduction in cardiovascular or all-cause mortality with tight glucose control [60]. A higher mortality was observed in the intensive glucose control arm of ACCORD, resulting in the premature termination of the glucose-lowering component of this study. Also, the occurrence of hypoglycemic episodes (total and major) was significantly higher in the intensive glucose control arms of all three studies [60].

The Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) study, DCCT's long-term follow-up study, were aimed at assessing the rate of micro- and macrovascular complications in diabetic patients and their relationships with hypoglycemic therapy. In the DCCT study, the incidence of cardiovascular events was not significantly associated with intensive insulin therapy. 93% of the original cohort of the DCCT study agreed to join the EDIC study with an 11-year follow-up period. The obtained results proved that intensive treatment was associated with reduced risk of any cardiovascular events by 42% during the 17-year follow-up ($p < 0.01$). Thus, DCCT (EDIC), and UKPDS showed that glycemic control in diabetic patients is important for the prevention of microvascular complications, but long-term follow-up is needed to demonstrate these effects [11].

In 2015, the American Diabetes Association and The European Association for the Study of Diabetes updated the positioned statement on the management of hyperglycemia of 2012, suggesting the need for strengthening the patient-centered approach to the management of diabetic patients [64]. They highlighted the necessity to individualize the range for glycemic control. They recommend to use the HbA1c range of 7.5–8% for elderly patients with diabetes and patients with a positive history of cardiovascular events, depending on their life expectancy, age, and social status [64]. A more tight target range (HbA1c 6.5–7.0%) may be used in patients with slow-onset diabetes, long life expectancy, and those without significant cardiovascular disease (CVD), if it can be achieved without hypoglycemia [64].

What tools may be used to control glycemia in patients undergoing myocardial revascul arization?

## 10. Hypoglycemic therapy in patients undergoing myocardial revascularization—the lack of evidence

A number of new classes of drugs for the treatment of diabetes and their effects on cardiovascular system have been studied well. However, there are limited data regarding in-hospital hypoglycemic therapy in patients undergoing myocardial revascularization. The concerns of medical community on this issue may be found directly in the headlines of recently published manuscripts. Hoogwerf addressed this issue in his article entitled "Perioperative management of diabetes mellitus: how should we act on the limited evidence?" [65]. Despite the fact that this article was published 10 years ago, and during this period new knowledge and evidence have been obtained, the question regarding optimal medical management of glycemia in patients undergoing coronary revascularization remains crucial. Recent guidelines on the management of diabetes [7–10] state the lack of evidence for using non-insulin hypoglycemic drugs in the perioperative period in diabetic patients.

Insulin remains the only approved perioperative method of hypoglycemic therapy. The current guidelines recommend use of basal insulin or basal-bolus regimen, and strongly discourage use of sliding-scale while a sliding schedule is strongly discouraged [8, 10].

Continuous intravenous insulin infusion is recognized as the preferred method for achieving and maintaining the glycemic control in critically ill patients [8–10]. The protocols for insulin infusion have been already developed and approved by diabetic communities [8–10]. They allow to adjust the rate of insulin infusion according to the glycemic levels. Insulin therapy should be initiated to treat persistent hyperglycemia, starting at a threshold of 180 mg/dL (10 mmol/L). Episodes of hypoglycemia should be noted in medical records and strictly monitored, since glucose level of 70 mg/dL require the changing of treatment regimen [8–10].

The multicenter DIGAMI, DIGAMI 2, HI-5 trials studied the intensity of the glucose control in ACS patients, including those undergoing PCI. Initially, DIGAMI reported low mortality in MI patients enrolled in the insulin therapy group [66]. However, the follow-up DIGAMI 2 trial with a double sample size and a more careful design did not show any advantages in the group of patients receiving intensive insulin therapy. Moreover, there were no significant differences in the rate of the composite endpoint (cardiovascular death/nonfatal myocardial infarction/stroke) between the intensive control group and the standard therapy group. The HI-5 study received similar results [66]. Since neither the DIGAMI 2, nor the HI-5 achieved differences in the control of glucose between the intensive management group and the control group, the effectiveness of insulin therapy for lowering glucose levels in ACS patients remains controversial. Combined data from these three studies confirmed that glucose-insulin-potassium infusion did not reduce mortality without the glucose control in diabetic patients with ACS (OR 1.07, 95% CI 0.85–1.36, $p = 0.547$) [66]. None of the protocols noted the improvements of the outcomes in patients with ST-segment elevation ACS after PCI, who received insulin or the intravenous glucose-insulin-potassium infusions [66].

The Japanese study, comprising 2148 patients who underwent PCI in the period from 2003 to 2012, showed an association between insulin use and increased rates of myocardial infarction and stent thrombosis [67]. The subgroup analysis of the FREEDOM trial, aimed at assessing outcomes of diabetic patients undergoing either CABG or PCI, reported that patients receiving insulin had a higher rate of major cardiovascular events [68]. Nevertheless, the use of insulin may be regarded as a marker of the severity and duration of diabetes, and does not reflect the true effects of therapy on the outcomes.

Currently, the discontinuation of long-acting drugs before surgical procedures is preferable, but there is no consensus on PCI, since the management of patients is commonly regulated by the local protocol [69]. There are available data suggesting safe and beneficial effects of long-acting oral hypoglycemic agents in PCI patients, resulting in better glycemic control and lower platelet activity [66].

The American and Canadian Diabetes Associations recommend to withhold metformin 24–48 h prior to CAG or PCI, and restart it 48 h after the procedure in the absence of significantly decreased GFR or later after the normalization of renal function [8, 10]. Although, recent studies showed the safety of continuing metformin therapy during the procedure, their statistical capacity is insufficient to change the current guidelines [10, 70, 71].

The recent study of patients with metabolic syndrome who received metformin for 7 days before PCI vs. the placebo group reported a lower rate of perioperative myocardial damage, estimated by elevated creatine phosphokinase-MB ($p = 0.008$) and troponin I ($p = 0.005$). According to the assessment of the 1-year prognosis, the incidence of major cardiovascular events (heart attack/stroke/cardiovascular death) was significantly lower in the metformin group (7.9 and 28.9%, respectively, $p = 0.001$) [72].

A randomized trial of 100 patients who received either 1000 mg of metformin or placebo after CABG in addition to standard insulin therapy, the metformin therapy was initiated 3 h after extubation and lasted for 3 days [70]. Based on the results, the mean dose of insulin, as well as the mean number of episodes of both hyper- and hypoglycemia, were significantly lower in the metformin group ($p < 0.05$). At the same time, the risk of acidosis in the metformin group did not increase [70].

There were some attempts to use metformin in non-diabetic patients undergoing coronary artery bypass grafting. The researchers concluded that the short-term use of metformin prior to CABG was relatively safe, but ineffective strategy for reducing periprocedural myocardial damage in non-diabetic patients [71].

The updated ADA 2017 guidelines noted that the SGLT2 inhibitors, despite their proven cardiovascular effects, cannot yet be recommended for the hospital use, and, therefore, should be avoided before surgical interventions [10].

## 11. Comprehensive risk factor control in diabetic patients in coronary procedures and interventions

In addition to the compensation of carbohydrate metabolism, multiple monitoring of risk factors in diabetic patients undergoing revascularization should be implemented and include achieving target levels of blood pressure (BP) and lipids, smoking cessation. The BARI-2D trial, focused at assessing coronary revascularization in diabetic patients, reported that both, the tight control over the main risk factors and intensive treatment management in diabetic patients according to the current guidelines, were associated with improved cardiovascular outcomes [23]. Based on the results of the study with a 20-year follow-up after CABG, long-term survival, and freedom from major cardiovascular events in diabetic patients followed CABG was lower. However, the monitoring of carbohydrate metabolism and other risk factors (target levels of lipids and arterial blood pressure, smoking cessation) appears to be significant for the prognosis in this group of patients [43]. Despite the improvements in achieving the goals of treatment for diabetes, it requires further control and monitoring, as only 14.3% of adult Americans with type 2 diabetes have target levels of HbA1c, blood pressure, and low-density lipoprotein cholesterol (LDL-C) [73].

To date, the evidence-based results of randomized clinical trials suggest that statin therapy reduces the incidence of cardiovascular events in diabetic patients [74, 75]. The protective cardiovascular effects of statins significantly outweigh the associated risk of developing diabetes mellitus [75]. The recent joint guidelines of the American Society of Cardiology and the Heart Association recognize diabetic patients aged 40–75 years as one of the four main groups of patients who would most likely benefit from statin therapy [23]. The guidelines of the American and European Society of Cardiologists recommend to initiate statin therapy in all patients who had myocardial infarction, regardless of the cholesterol level [76]. However, there are several studies reporting that low levels of low-density lipoprotein cholesterol (LDL cholesterol), regardless of hypolipidemic therapy, are associated with increased in-hospital mortality in ACS patients, including those undergoing PCI. The results of a study, comprising of 9032 patients with myocardial infarction who underwent primary PCI in 68 centers in Tokyo, convincingly showed that statin therapy significantly reduced in-hospital mortality, even in patients with low LDL cholesterol and those with diabetes [77].

A large retrospective analysis, including 16,192 patients undergoing CABG, demonstrated that the use of statins, regardless of diabetes and other risk factors, was associated with a significant reduction of in-hospital mortality in five logistic regression models [78]. Importantly, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and calcium antagonists did not show any significant correlations with the outcomes followed CABG [78]. However, there are available data on beneficial effects of statins on reducing the incidence of atrial fibrillation and cognitive impairment after CABG, including patients with diabetes mellitus [48, 78].

Undoubtedly, patients with diabetes, undergoing revascularization, need to achieve the target levels of systolic blood pressure < 140 mm Hg and diastolic blood pressure < 90 mm Hg. These target levels are required to reduce cardiovascular risk according to the recent statement of the American Heart Association and American Diabetics Association. Moreover, the AHA/ADA guidelines recommend to use ACE inhibitors and angiotensin II receptor antagonists for treating arterial hypertension in diabetic patients [54].

Thus, we may conclude that the negative impact of diabetes on the prognosis after myocardial revascularization and the need to achieve the target ranges of carbohydrate metabolism, as well as the comprehensive cardiovascular control are evident in treating diabetic patients. However, the benefits of the intensive glycemic management remain controversial. Other treatment strategies, such as continuing prescribed hypoglycemic drugs, including long-acting ones, should be considered only in patients undergoing PCI, but not in those who are referred to elective open-heart surgeries. Currently, the issues that require further research have been highlighted in our review and, in a few years, new clinical trials will provide new insights for medical community dealing with diabetes and coronary artery diseases.

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