

REVIEW ARTICLES

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Myocardial revascularization in patients with coronary artery disease and diabetes mellitus

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Abstract

Background: Diabetes mellitus (DM) is one of the most crucial risk factors for morbidity and mortality from coronary heart disease (CAD) in the contemporary world. The prevalence and rapid progression of atherosclerotic lesions leading to worse survival is a defining feature of the course of CAD in patients with DM. Clinical manifestations of CAD often call for revascularization in patients with DM. The contemporary data regarding efficacy of the coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) in patients with CAD and concomitant DM are summarized in the review.

Conclusions: Worse survival prognosis in case of CAD with concomitant DM is associated with systemic atherosclerosis, presence of a number of concomitant risk factors, as well as masked clinical manifestations of ischemia and myocardial infarction common for the patients with DM. The combination of CAD and DM once again proves the benefit of the long-term use of drugs for the secondary prevention of cardiovascular events. From the standpoint of evidence-based medicine the optimal method of revascularization in CAD patients with multivessel coronary artery disease and concomitant DM is CABG surgery. In FREEDOM study surgical myocardial revascularization reduced the number of endpoints compared to PCI. In the case of PCI it is advisable that eluting stents reducing the likelihood of restenosis and the need for repeated revascularization be used.

Key words: diabetes mellitus, coronary artery disease, coronary artery bypass grafting.

Introduction

Diabetes mellitus (DM) is one of the most crucial risk factors for morbidity and mortality from coronary heart disease (CAD) in the modern world. 25-30% of patients with acute coronary syndromes are diagnosed with DM [27]. Clinical manifestations of CAD develop earlier in patients with DM and are associated with a worse prognosis compared with patients without diabetes. CAD associated mortality in patients with DM is two times higher than that in patients without diabetes [31]; CAD is the cause of death of three out of four patients with DM [25]. This allows characterizing DM as an equivalent of CAD with already suffered myocardial infarction (MI) in terms of the risk of coronary events [18]. Clinical manifestations of CAD often call for a specific medical therapy and revascularization in patients with DM. On the other hand, concomitant DM is present in almost 40% of patients with CAD who undergo coronary artery bypass grafting (CABG) [27]. The existing evidence base and existing clinical experience allow us to summarize the current state of the problem of myocardial revascularization in patients with stable coronary artery disease and diabetes.

Diagnosis and the course of CAD in patients with DM

Rapid progression and prevalence of atherosclerotic lesions in the presence of DM is accounted for by a number of adverse effects associated with hyperglycemia, insulin resistance and dyslipidemia. These include, in particular, enhancement of lipid uptake by macrophages, leading to the formation of foam cells, endothelial dysfunction, platelet activation, increased activity of proteolysis processes, and stimulation of smooth muscle cell proliferation, fibrosis and systemic inflammation [29]. Insulin resistance and hyperinsulinemia are associated with other risk factors for CAD, such as impaired glucose tolerance, hypertriglyceridemia, a decrease in high-density lipoprotein cholesterol, and arterial hypertension. At the same time, isolated hyperinsulinemia has recently been considered an independent cardiovascular risk factor [33].

Patients with DM are more likely to have lesions of the left coronary artery and multivessel coronary arteries; they also have more lipid-rich and prone to rupture atherosclerotic plaques [27]. Factors that can determine worse survival prognosis of diabetic patients are diffuse atherosclerotic lesions of the small coronary arteries, the presence of many

associated risk factors, in particular kidney damage, and masking of clinical manifestations of ischemia in patients with DM. Consequently, even with the expansion of choice of medical and interventional treatment, the prognosis in patients with DM and already formed cardiovascular disease is significantly worse than in those without it.

Methods to diagnose CAD in patients with DM do not differ essentially from those used in patients without diabetes. Patients with DM often have symptoms atypical for ischemia, or painless course of CAD. The main non-invasive method of examination in the presence of chest pain is a stress test on a bicycle ergometer or treadmill; out-patient ECG monitoring may have additional significance in certain situations (for example, during nighttime or morning painful attacks). In patients with DM the initial probability of CAD is higher than in those without it. This, in turn, may affect the informative value of instrumental methods of CAD diagnostics. For example, with a positive test result in a patient with DM and atypical pain, the probability of CAD is higher than in a patient without diabetes. However, obtaining a negative result in many cases allows discontinuing the examination [33]. In doubtful situations, it is possible to use the most sensitive and highly specific methods for CAD diagnostics and myocardial viability assessment; in particular, single-photon emission computed tomography (SPECT) with thallium-201 or sestamibi, or stress echocardiography with exercise or dobutamine stress echocardiography.

The potential for reducing CAD associated mortality in patients with type 2 diabetes largely depends on how well risk factors are being corrected, including the use of modern antihypertensive and hypolipidemic agents [16]. The combination of CAD with DM is an additional strong reason for the secondary prevention of cardiovascular events with antiplatelet agents, beta-blockers, statins and renin-angiotensin system blockers [34]. Yet, the greatest hopes for the improvement of the course of CAD in patients with DM are associated with surgical or endovascular myocardial revascularization. Nevertheless, even in the case of percutaneous coronary interventions (PCI) or coronary artery bypass grafting (CABG), the survival prognosis of patients remains worse compared with those without diabetes [29].

Patients with DM who have undergone CABG in our clinic demonstrated hemodynamically significant stenoses of the right and circumflex coronary arteries more often. In these patients a greater number of postoperative complications were recorded (in particular, nephropathy and postoperative atrial fibrillation) compared with those without DM [1]. It is the presence of a diffuse lesion of the coronary bed that explains the high probability of restenosis caused by neointimal hyperplasia following PCI in the presence of DM. To a certain extent the frequency of restenosis was reduced due to the introduction of eluting stents (with a drug coating). However, even with the widespread use of this modern technology of endovascular treatment, DM is associated with poor clinical outcomes. DM appeared one of the most powerful predictors of stent thrombosis in a meta-analysis of 47 studied factors [12].

The information on the effect of DM on the outcomes of interventions is mainly based on the data from observational studies, registers, retrospective analyses of subgroups of patients with DM in large controlled studies of the effectiveness of revascularization, as well as studies comparing the effectiveness of PCI and CABG. Only in some studies, though, interventional treatment of CAD in patients with DM was given special consideration to.

Revascularization or medical treatment?

Generally, the indications for myocardial revascularization in patients with DM do not differ drastically from those in patients without it. In particular, a meta-analysis of nine randomized clinical trials involving 9904 patients with acute coronary syndrome did not reveal any dependence of the benefit of revascularization in the presence of DM [28]. At the same time the absolute risk reduction was larger with concomitant diabetes compared with patients without DM.

BARI 2D study included patients with type 2 diabetes and hemodynamically significant stenosis of at least one coronary artery. Half of the patients had stable angina, 10% had unstable angina, and 18% did not have angina or its equivalents. Patients with indisputable indications for revascularization (for example, multi-vessel lesion with LVD) were not included. In all cases, intensive drug therapy was carried out to correct hyperglycemia, dyslipidemia, hypertension, reduce angina, as well as modify lifestyle. On evaluating the coronary angiography data, the cardiologist chose the potentially most appropriate method of revascularization: PCI or CABG followed by randomization into groups of drug treatment or revascularization. Consequently, PCI was mainly performed in patients with a lesion of one or two vessels (two-thirds of the participants), while patients with a three-vascular lesion underwent CABG [15].

At the same time, among high-risk patients selected for CABG surgery, revascularization reduced the incidence of major cardiovascular events (22% versus 31%, $p = 0.01$) and non-fatal MI (7% versus 15%, $p < 0.01$). Thus, for the first time it was shown that in stable patients with coronary atherosclerosis, CABG operation reduced the risk of the future non-fatal MI, while in the low-risk patients selected for PCI, immediate revascularization did not improve outcomes. The results obtained in BARI 2D study agreed with the data from COURAGE study and other studies in which most patients did not have DM [4, 9].

It is worth noting that BARI 2D study did not include patients with initial coronary atherosclerosis (without convincing indications for revascularization) on the one hand, and, on the other hand, patients with severe symptoms or pronounced stenotic coronary arteriosclerosis (therefore, absolute indications for revascularization). Thus, the results of this study are most relevant to patients with moderate or stable symptoms and /or moderately pronounced atherosclerotic changes in the coronary bed. Moreover, approximately 40% of patients randomized for drug treatment, during 5 years of follow-up, were actually revascularized due

to the progression of angina, acute coronary syndrome or severe myocardial ischemia. Only a third of the patients in the PCI group had eluted stents implanted; in most cases, conventional metal stents were used [31].

Surgical revascularization of percutaneous intervention?

BARI 2D study did not attempt to compare the effectiveness of CABG and PCI, because the groups of patients who used various methods of revascularization differed significantly in angiographic characteristics. The first attempt to answer this question was made in the original BARI study, in which 1.829 patients (mostly with unstable angina and multivessel CAD) were randomized to CABG or PCI groups (at that time – balloon angioplasty) [6]. No differences in death rates or MI were revealed in the compared groups in this study. However, in patients with concomitant DM such differences were found. In particular, the mortality of patients with diabetes and CAD with lesions of one or two vessels of coronary arteries during 5 years of the follow-up was 35% in the PCI group and 19% after CABG [7]. CABG was generally associated with significantly better survival over five (80% vs. 67%) and ten years (respectively, 58% vs. 46%, $p = 0.025$) compared with balloon angioplasty [7,8]. Undoubtedly, the use of CABG was determined by the use of arterial mammary shunts in 81% of cases. The results of BARI study and some retrospective analyses showed that the presence of DM can affect not only the outcomes of revascularization interventions, but also the choice between CABG and PCI.

The results of retrospective analyses also testified to the possible advantages of CABG in comparison with PCI in terms of the effect on mortality within 5 years in patients with CAD and DM [10]. The use of PCI with stent implantation is often associated in patients with DM with the formation of restenosis. In CARDia study involving 510 patients with DM during a one year observation, the use of stents was accompanied by a greater incidence of restenosis and repeated revascularization compared with CABG [24]. Despite the obvious limitations of retrospective analyses, the existing evidence base testified in favor of performing CABG (and not PCI) as a more reliable method for myocardial revascularization in patients with three-vascular lesion or stenosis of the left coronary artery. In particular, in the subgroup of 452 patients with DM and multivessel lesions of coronary arteries in the SYNTAX study with a 5-year follow-up, no differences between the CABG and PCI groups were found in terms of incidence of “large” cardiovascular complications; however, the need to repeat revascularization was more common in the PCI group [27].

It can be assumed that concomitant DM does not affect the patency of arterial (mammary) shunts, in contrast to venous shunts, where rapid progression of atherosclerotic lesions was observed [32]. Moreover, a lower incidence of non-fatal MI in BARI-2D study [15] revealed that bypass surgery, unlike endovascular interventions, helps to prevent the progression of coronary artery lesions and / or rupture

of atherosclerotic plaque in proximal regions [2]. However, despite these arguments, the percentage of PCI in patients with diabetes continued to increase. Obviously, this paradoxical phenomenon was brought about by the advancement of the eluting stents technology, as well as a frequent instant implementation of angiography and PCI, without a proper discussion and giving the patient full information to make a reasonable decision [21].

A FREEDOM study conducted by the United States National Heart, Lung, and Blood Institute randomized patients with DM and multivessel CAD into PCI groups with implantation of eluting stents (such as sirolimus or paclitaxel) or CABG surgery (2.9 shunt per patient, 94.4 % of cases used arterial shunts) [14]. The study included patients with hemodynamically significant stenosis (more than 70%) of two or more coronary arteries, but without stenosis of the left coronary artery trunk. Only about a quarter of patients had previously suffered MI, in the overwhelming majority of cases, the left ventricular (LV) ejection fraction (EF) was preserved (i.e., there were no convincing indications for surgical revascularization). The observation lasted at least two years, on average – 3.8 years. All patients were prescribed modern medical therapy to control low-density lipoprotein cholesterol level (target value less than 70 mg%), blood pressure (less than 130/80 mm Hg) and glycosylated hemoglobin (less than 7%). The primary endpoint was the sum of death outcomes, non-fatal MI, or stroke.

A total of 1900 patients were included (mean age 63.1 ± 9.1 years, 29% – women), with 83% having a three-vessel lesion. The frequency of reaching the primary endpoint after CABG was 30% less: in the CABG group it made up 18.7%, after PCI – 26.6% ($P = 0.005$). The effect of CABG was achieved by reducing MI frequency (10.9% versus 16.3%, $P < 0.001$) and death from any cause (6.0% versus 13.9%, $P = 0.049$). Yet, strokes developed more often in the CABG group than after stenting (5.2% vs. 2.4%, $P = 0.03$), mainly occurring in the early postoperative period.

FREEDOM study was the most significant stage in the discussion on the choice of the optimal method of revascularization in patients with DM. CABG surgery provided better results than PCI due to a decrease in the frequency of end points [14]. A little later, similar results were obtained in VACARDS study [23], where a comparison of CABG and PCI was also conducted in patients with DM. Due to the early termination of the study, a total of only 198 patients were randomized. Deaths, or non-fatal MI cases occurred in 18.4% of patients in the CABG group and 25.9% in the PCI group ($P < 0.05$).

A certain limitation to the use of data from FREEDOM study was a relative “mildness” of patients in terms of the frequency of previous MI, severity of LV dysfunction, and clinical manifestations of heart failure. To a certain extent, this limitation was overcome in a recently published analysis of outcomes in 11.518 patients with LV ischemic dysfunction, conducted as a part of a register in the Canadian province of Alberta [19]. The difference between CABG and PCI in terms of the overall influence on mortality rate was

evident in patients with DM (10.7 and 15.7% respectively, $P = 0.0001$) and was absent in patients without it (8.4 and 8.7%, unreliable differences). Among 2387 patients with DM, “matches” with similar clinical characteristics were specifically selected who underwent CABG or PCI [26]. The frequency of “major” cardiovascular complications, as well as death from all causes was greater in the cohort of patients with EF less than 35% and 35-49%. The incidence of stroke did not differ in the CABG and PCI groups, regardless of EF indicator. PCI was associated with a greater incidence of MI in the cohort of patients with low EF, whereas repeated revascularization was more often recorded after PCI in cohorts with EF less than 35% and 35-49%. The authors concluded that CABG is more expedient in terms of the effect on the risk of cardiovascular complications and the survival of patients with DM and LVD.

Favorable effects of CABG compared with PCI were also confirmed in a recently published analysis of the results of treatment of patients after acute coronary syndrome in real clinical practice [30]. In a systematic analysis of the results of interventional treatment of 13114 patients with type 2 diabetes cases of major adverse events, repeated revascularization and MI were observed more often in the PCI group than after CABG [11]. It should be noted that groups of patients with and without DM do not differ in the incidence of early stent thrombosis; at the same time, DM is associated with a greater incidence of late thrombosis compared with patients without diabetes [38].

Obviously, the type of stents used can have a significant impact on the results of PCI in patients with DM. In particular, in the New York State register, the use of everolim-

us-type stents was associated with a similar risk of death, a higher risk of MI (in case of incomplete revascularization) and repeated revascularization, and a lower risk of stroke compared to isolated CABG [3]. In general, the existing evidence base testifies in favor of CABG, rather than PCI, in patients with DM and multivessel CAD [22, 36]. Basing on the available data, patients with DM should be informed about the benefits of CABG for improvement of survival prior to coronary angiography. If there is a concomitant pathology which causes an increased risk of surgery, an individualized decision regarding the type of revascularization should be made by a multidisciplinary team of specialists based on a comparison of the advantages and disadvantages of various methods [20, 27].

Consensus recommendations and contradicting aspects of patient management

Feasibility of sensitive heart stress-visualization methods to detect MI has not yet been proved in asymptomatic patients with DM who have no past history of coronary events [17, 37]. In such cases optimal drug therapy aimed at the primary prevention of cardiovascular events remains the method of choice [34]. Detection of LV dysfunction, high-risk criteria according to the exercise test, as well as cases of insufficient effectiveness of drug therapy form the basis for coronary angiography in patients with anginal attacks (fig. 1). Basing on the results of BARI 2D study, patients with one or two vascular lesions of coronary arteries associated with stable manifestations of MI can continue conservative treatment, while in case of destabilization of ischemia or emergence of disabling symptoms (angina at low loads), surgical

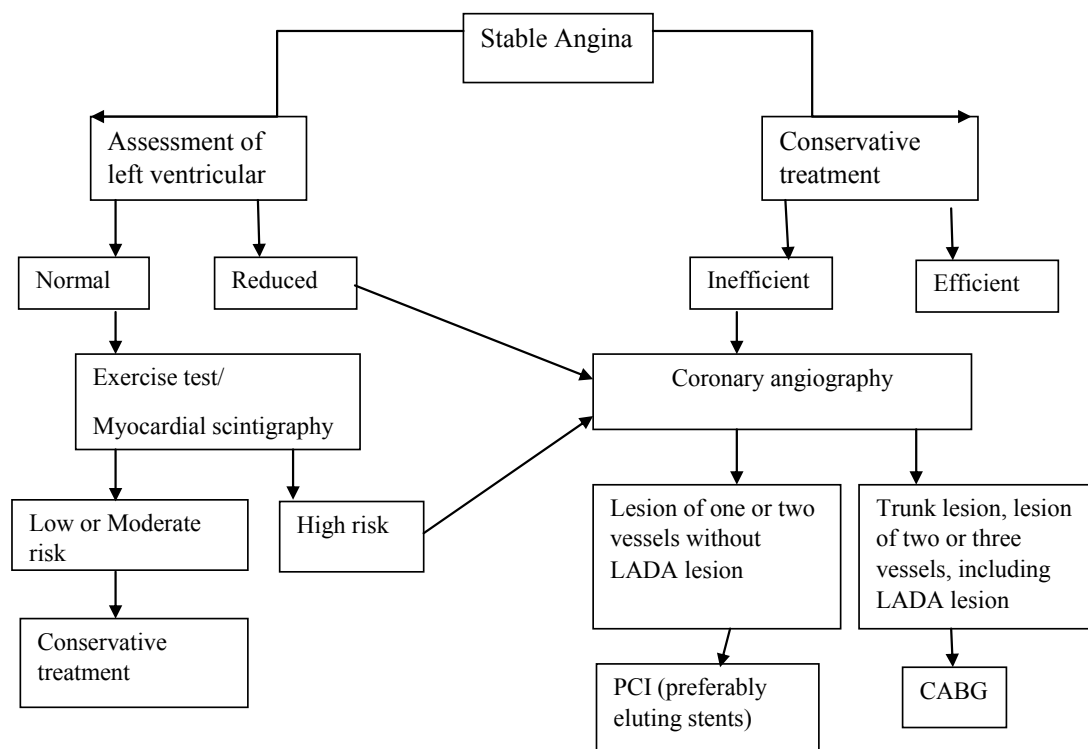


Fig. 1. Algorithm for management of patients with stable angina with / without concomitant DM. LADA – Left Anterior Descending Artery.

myocardial revascularization or PCI should be considered. Finally, in patients with multivessel CAD in the presence of DM, surgical myocardial revascularization has advantages over PCI, which has been primarily, indicated by the results of BARI 2D and FREEDOM studies [14, 15].

In any case, the decision on the treatment strategy and the choice of revascularization method in particular should be made taking into account the patient's opinion, not only the information about the anatomy of coronary bed and the point of view of the attending physicians. For many patients, objective, balanced information about the expected length of stay in the clinic, recovery time, quality of life, risk of stroke, as well as the possible need for re-revascularization is crucial to make a final decision (tab. 1).

Table 1

The advantages and disadvantages of various treatment strategies for patients with moderate CAD with concomitant DM (adapted from [31])

Compared criteria	Drug therapy	PCI	CABG
Symptom control	Moderate	Good	Good
Primary or repeated revascularization over 5 years	42% (BARI 2D study)	30%	9%
Repeated revascularization over 1 year	-----	12-20%	2-6%
Mortality risk	Reference	Similar	Similar
MI risk	Reference	Similar	Lower
Non-fatal stroke	Not known	0.4-0.9%	2.5-2.8%
Hospital stay and rehabilitation	Reference	Days	Weeks and months
Quality of life in a year	Reference	Similar	Better
Extent of revascularization	-----	Moderate	Good
Cost-effect ratio:			
Over 4 years	Reference	Worse	Worse
Over life span	Reference	Worse	Better

In the European recommendations for myocardial revascularization in 2018, a special section is devoted to the features of treatment of patients with DM [27]. First of all, this document clearly states that anatomical indications for revascularization in patients with DM are the same as in patients without it. In stable patients with CAD multivessel coronary artery disease and / or lesion of the left coronary artery is an argument in favor of CABG, rather than PCI.

Management problems and worse outcomes in patients with DM who previously underwent surgical myocardial revascularization or endovascular interventions are due to the progressive nature of atherosclerotic vascular lesions, severe endothelial dysfunction, platelet activation and blood clotting disorders [34]. These pathophysiological features determine the priorities of additional drug therapy after revascularization, with particular attention to the treatment of associated diseases and correction of risk factors [16]. However, there has been no convincing data on the effect of glycemia on the frequency of restenosis after PCI or the pa-

tency of shunts after CABG surgery so far. Special attention is given to the assessment of renal function before angiography in patients receiving metformin, with the suspension of the drug for 48 hours before the study in the presence of renal failure, and in other patients – in case of deterioration in renal function after angiography [27].

Undoubtedly, the use of renin-angiotensin system blockers, beta-blockers, antiplatelet agents after revascularization in patients with DM seems expedient. Aggressive control of the lipid profile by drugs from statin group, whose dose in patients with a very high level of risk (including patients with CAD and DM) is determined depending on the achievement of the target level of low-density lipoprotein less than 1.8 mmol/l also seems reasonable [13, 35].

European Survey Study on Coronary Revascularization assessed the potential impact of the presence of DM on the physician's choice of drug treatment or revascularization. It has been found that DM was not included in the list of the main factors determining the physician's decision in case of a stable course of CAD [5]. It should be noted that when choosing the revascularization method for patients with DM high probability of restenosis after PCI should be taken into account [34].

Conclusions

The prevalence and rapid progression of atherosclerotic lesions is a defining feature of the course of CAD in patients with DM. Worse survival prognosis in case of concomitant DM is associated with systemic atherosclerosis, presence of a number of concomitant risk factors, as well as masked clinical manifestations of ischemia and MI common for patients with DM. The combination of CAD and DM once again proves the benefit of the long-term use of drugs for the secondary prevention of cardiovascular events. From the standpoint of evidence-based medicine the optimal method of revascularization in CAD patients with multivessel coronary artery disease and concomitant DM is CABG surgery. In FREEDOM study surgical myocardial revascularization reduced the number of endpoints compared to PCI. In the case of PCI it is advisable that eluting stents reducing the likelihood of restenosis and the need for repeated revascularization be used.

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