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Coronary and peripheral arteries revascularization in patients with diabetes mellitus: a cardiologist's view

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Abstract

Diabetes mellitus (DM) is one of the main risk factors for the development of myocardial infarction, stroke and lower-limb amputation that are associated with the acceleration of vascular arteriosclerotic damage. At the certain stage of the atherosclerosis and its complications development, indications for the revascularization appear. In recent years, there has been significant progress in the development and investigation of revascularization methods along with concomitant pharmacotherapy, especially in patients with DM. Using the PubMed / MEDLINE database, we analyzed research articles, meta-analyzes and reviews published over the past 5 years in leading peer-reviewed journals on the problem of coronary and peripheral artery revascularization in patients with DM. This review article provides information on the choice of the myocardial revascularization method in patients with ACS, stable coronary heart disease, peripheral arterial disease of the lower extremities, carotid artery stenosis and pharmacological therapy for the prevention of atherosclerosis complications in patients with DM.

Key words: diabetes mellitus, coronary heart disease, coronary artery bypass grafting, percutaneous coronary intervention, peripheral arterial disease, carotid artery stenosis.

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Diabetes mellitus (DM) is one of the main risk factors for the development of cardiovascular diseases (CVD), including coronary heart disease (CHD), stroke, peripheral arterial disease (PAD), carotid artery disease, which are associated with vascular damage due to atherosclerosis progression [1]. Patients with DM significantly more often undergo coronary and peripheral arteries revascularization, including repeat surgery, compared with general population [2,3]. Therefore, the correct choice of treatment method for patients with atherosclerosis and DM is of primary importance, which include pharmacological therapy, interventional and surgical procedures that have been actively improving over the last years [4,5].

The objective of this study is to collect and review the new data on coronary and peripheral artery revascularization and concomitant pharmacological treatment in patients with DM.

The importance of coronary and peripheral artery studies in patients with diabetes mellitus

CHD in patients with DM is characterized by diffuse rapidly progression with multivessel involvement and arterial calcification, that often requires coronary revascularization in addition to optimal pharmacological treatment. Atherosclerotic plaques in patients with DM exhibit more vulnerable features due to lipid-rich core, macrophage accumulation, and thin fibrous cap, indicating vascular plaque instability [6].

The results of coronary angiography in patients with DM poorly correlate with the hemodynamic (ischemic) significance of atherosclerosis. Fractional flow reserve assessment is more accurate invasive technique that reveals significant hemodynamically stable coronary stenoses that cause myocardial ischemia. The visualization of the myocardium with single-photon emission computed tomography is the non-invasive method that allows to detect coronary stenoses of sufficient hemodynamic severity to induce myocardial ischemia. However, both of these complex and expensive methods do not provide the same degree of accuracy in patients without ischemia with and without DM. Therefore, delayed revascularization in patients without ischemia (ischemia driven revascularization strategy) can be not as safe for patients with DM as for patients without DM.

This fact can be partially explained by high prevalence of microvascular dysfunction, fast diffuse atherosclerosis dysfunction and atherosclerotic plaques features (greater necrotic core and larger calcium content) in patients with DM [7].

The degree of atherosclerotic lesions can be determined invasively using intravascular ultrasound or non-invasively using coronary computed tomographic angiography with the assessment of the coronary artery calcium score. The increase of the coronary artery calcium score by 1 step (from 1–99 to 100–399 and to ≥400 Agatston units) is associated with the progressive increase of the relative risk of death [8].

The determination of the intima — media thickness of the carotid arteries using ultrasound scanning in patients with DM does not increase the predictive accuracy for CHD or cardiovascular complications compared with the coronary artery calcium score. On the contrary, large atherosclerotic plaques of the carotid arteries can serve as independent predictors of CVDs and its complications (CHD, ischemic stroke, peripheral arterial disease) [9].

The ankle-brachial index is currently used for the detection of PAD, and the value of <0.90 (or >1.40) is associated with the increased risk of all-cause and cardiovascular mortality in patients with DM [10].

Myocardial revascularization in patients with acute coronary syndrome and diabetes mellitus

The pathogenetic mechanisms of the atherosclerosis development in patients with DM go far beyond the hyperglycemia and lead to frequent stenosis of the left main coronary artery, multivessel coronary artery disease (MVD), diffuse coronary artery disease with frequent involvement of its distal branches [1]. Myocardial revascularization using percutaneous coronary intervention (PCI) is the primary treatment choice for patients with ST-segment elevation acute coronary syndrome (ACS) regardless of the presence of DM [11]. However, PCI is not the best choice for the revascularization of arteries that were not associated with the development of ACS in patients with DM and MVD. In the British Columbia, Canada, all coronary revascularization procedures between 2007 and 2014 in 2.947 patients with ACS, DM and MVD were analyzed.

The frequency of major adverse cardiac or cerebrovascular events — all-cause death, nonfatal myocardial infarction (MI), and nonfatal stroke was lower after artery bypass grafting (CABG) surgery compared with percutaneous coronary intervention (PCI) (4.3% versus 8.2%; $p<0.01$) after the first 30 days and 3.3 years (20.8% versus 33.4%, respectively, $p<0.01$). Patients after ACS also showed lower frequency of repeat post-discharge revascularization (8.2% versus 22.6% after

PCI, respectively, p<0.01), MI (9.9% versus 17.6%, respectively, p<0.01) and all-cause mortality (12.4% versus 22.3%, respectively, p<0.01), and there were no significant differences in the incidence of stroke (6.2% versus 5.8%, respectively; p= 0.97) [12].

Current European recommendations for coronary revascularization in patients with DM with ACS without ST-segment elevation are mainly based on the studies on the treatment of stable CHD and expert opinion, because the necessary studies with high-level of evidence are clearly insufficient [11]. In the United States, only about ⅓ of patients with DM and MVD undergo CABG during ACS without ST-segment elevation [13]. In the clinical practice, recommendations for myocardial revascularization in patients with stable CHD are also used in patients with ACS. Therefore, the pathophysiology of atherosclerosis in patients with DM is not considered — diffuse long coronary artery lesions. It is thought that CABG is more effective in patients with DM, since PCI targets only the most visible plaques, leaving untreated other lesions that can cause new atherothrombotic events, especially along with pro-inflammatory state after ACS. In addition, patients with DM usually have many other comorbidities (arterial hypertension (AH), chronic kidney disease, heart failure), higher risk of complications after PCI — stent thrombosis and restenosis, which contributes to the prognosis after ACS [14].

Myocardial revascularization in patients with stable coronary heart disease and diabetes mellitus

Stents or Bypass Surgery for the Management of Coronary Heart Disease?

Several studies have compared CABG and PCI in patients with DM and stable CHD. CABG led to an increased risk of cardiovascular adverse events, especially stroke, in the first days and months after the procedure, but in the long-term it was associated with lower incidence of MI and repeated coronary revascularization. The most famous randomized trial FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) showed significant reduction of the amount of major cardiovascular complications (all-cause mortality, MI, and stroke) in patients with DM who underwent CABG compared with PCI during a mean follow-up period of 3.8 years (18.7% versus 26.6%, p=0.005). Longer follow-up for 7.5 years was associated with the decrease of all-cause mortality in patients after CABG compared with PCI (18.3% and 24.3%, respectively, p= 0.01) [15]. The meta-analysis of 11 randomized trials (n= 11518), including FREEDOM data, demonstrated higher 5-year mortality rate in patients with DM and stable CHD after PCI compared with CABG (relative risk (RR) — 1.48 with 95% confidence interval (CI) CI from 1.19 to 1.84, p= 0.0004) [16].

Later, large retrospective study using the database of the province of Canada, Ontario from 2008 to 2017 compared the outcomes of PCI (n= 4519) and CABG (n= 9716) in patients with DM and MVD [17]. In order to eliminate the initial differences between treatment groups, the propensity score matching method was used and allowed to obtain 4301 pairs of patients that were well balanced in 23 parameters. PCI and CABG groups showed similar frequency of early mortality (2.4% versus 2.3%, respectively; p= 0.721), but after 5.5-year follow-up CABG was superior to PCI in all-cause mortality (RR 1.39, 95, CI from 1.28 to 1.51) and the total incidence of major cardiovascular complications (RR — 1.99, 95%, CI from 1.86 to 2.12).

One of the latest meta-analysis of 9 randomized clinical trials of revascularization in patients with CHD and type 2 DM (n=4566) showed that PCI compared with CABG was associated with higher all-cause mortality frequency (RR 1.41, 95% CI 1.22 to 1, 63, p<0.001), cardiac death (RR — 1.56 with 95% CI from 1.25 to 1.95, p<0.001) and repeated revascularization (RR — 2.68 with 95% CI from 1.86 to 3.85, p<0.001) with a comparable frequency of MI (RR 1.20 at 95% CI 0.78 to 1.85, p=0.414) and lower risk of stroke (RR 0.51 at 95% CI from 0.34 to 0.77, p= 0.001). A cumulative meta-analysis of all-cause mortality showed that the differences between CABG and PCI groups reached statistical significance after 3 years of follow-up [18].

Another relatively new meta-analysis of 3 randomized and 5 observational studies (n= 3835) compared 10-year outcomes in patients with type 2 DM and CHD with stenosis of the trunk of the left coronary artery after PCI and CABG. Patients after CABG had lower mortality (RR — 0.85 at 95% CI from 0.73 to 1.00, p= 0.05), the frequency of MI (RR — 0.53 at 95% CI from 0.35 to 0.80, p= 0.002), repeated revascularization (RR 0.34 at 95% CI 0.26 to 0.46, p= 0.00001) and revascularization of the target coronary artery (RR 0.26 at 95% CI from 0.18 to 0.38, p= 0.00001). After 10-year follow-up, the summary of primary adverse cardiac and cerebrovascular events was also significantly lower in patients after CABG compared with

PCI (RR 0.67, 95% CI 0.49 to 0.92, p=0.01). However, CABG was associated with significantly higher risk of stroke (RR 2.16, 95% CI 1.39 to 3.37, p= 0.0007) [19].

Most studies showed that CABG was superior to PCI in patients with DM and CHD. However, the rapid improvement of PCI technology, drug-eluting stents design, and image-guided stent placement in combination with modern antiplatelet and lipid-lowering therapy contribute to the continuous enhancement of PCI results. Currently, there are no prospective studies comparing the latest PCI technologies and CABG in patients with DM.

Which coronary stents are best?

In recent years many studies have compared the results of various stents types implantation. Patients with DM and CHD did not have difference in mortality, MI, and repeated revascularization when using sirolimus-eluting stent or zotarolimus-eluting stent [20]. The ISAR-TEST 5 trial assessed the results of 10-year clinical outcomes in pre-defined subgroups of patients with or without DM randomized to polymer-free sirolimus- and probucol-eluting stent (n=2002) that provides effective drug release without polymer versus zotarolimus-eluting stent (n=1000) implantation [21]. Both new generation drug-eluting stents showed comparable clinical outcomes regardless of the presence of DM and the strategy of polymer covering. It has been shown that the frequency of adverse events after PCI in patients with DM was significantly higher compared with patients without DM and that it increases over time.

Biodegradable-polymer drug-eluting stents provide controlled drug release and complete polymer degradation over time. As a result, the risk of chronic inflammation and atherosclerosis progression decreases that is crucial for patients with DM. The efficacy and safety of the new drug-eluting stents in patients with DM remained unclear for a long time. Bavishi C. et al (2020) presented the combined results of 11 randomized controlled trials of PCI involving 5190 patients with DM and CHD [22]. The average follow-up was 2.7 years, there were no significant differences in the efficacy of revascularization, all-cause mortality, cardiovascular mortality, and MI rates between the groups of patients after the implantation of biodegradable-polymer drug-eluting stents and polymer durable drug-eluting stents. The incidence of stent thrombosis was also similar between the groups (1.66% versus 1.83%, respectively; RR 0.84, 95% CI 0.54 to 1, 31, p=0.45). The meta-regression analysis did not reveal any associations between DM that require insulin treatment and the long-term effectiveness of PCI or thrombosis of the studied stent types.

Recently the comparison of 10-year clinical outcomes following implantation of new generation biodegradable-polymer sirolimus-eluting stents (Yukon Choice PC, n= 1299) and polymer durable everolimus-eluting stents (Xience, n= 652) in patients with and without DM was completed [23]. After 10-year follow up, patients with DM had significantly higher incidence of major adverse cardiac events compared with patients without DM (RR 1.41, 95% CI 1.22 to 1.63, p<0.001) that did not depend on the type of stent. The incidence of definite / probable stent thrombosis was 2.3% in patients with DM and 1.9% in patients without DM (RR 1.27 with 95% CI 0.34 to 2.60, p= 0.52) with no significant differences between the compared stents. Consequently, clinical outcomes in patients with DM after PCI using various new generation drug-eluting stents are significantly poorer compared with patients without DM, and the incidence of adverse events is constantly increasing up to 10 years. So far, the use of new-generation drug-eluting stents in patients with DM does not allow to achieve similar to CABG outcomes, especially when the revascularization of coronary arteries is incomplete.

Is the assessment of multivessel coronary lesions severity necessary?

The assessment of coronary atherosclerosis severity according to the SYNTAX score includes the number of lesions, their complexity and functional significance. The SYNTAX score identifies patients with low (≤22 points), medium (23–32 points), and high (≥33 points) risk, suggesting better outcomes after CABG versus PCI in patients with high risk. However, the results of the FREEDOM study [15] questioned the implementation of the SYNTAX scale for the determination of myocardial revascularization strategy in patients with DM and MVD, and confirmed the superiority of CABG in this category of patients regardless of the SYNTAX score. The FREEDOM project did not reveal significant association between the benefits of CABG versus PCI and SYNTAX scores when enrolling patients into the study [24].

CABG, given that it can be performed with very low risk of complications, represents fundamentally different type of revascularization compared with PCI. By providing the new segments of the coronary arteries after each bypassed stenosis, CABG has 3 important effects: 1) perfusion through the graft, similar to PCI, but with the additional distal protection from the development of new lesions of the proximal and middle segments of the arteries; 2) the improvement of endothelial function due to the addition of nitric oxide production by the arterial grafts that can aggravate CHD due to the development of endothelial dysfunction and chronic inflammation [25]; and 3) the development of new collaterals in the recently perfused myocardium [26]. The consequences of the blood flow cessation after successful CABG are significantly less severe compared with PCI that is associated with high morbidity and mortality [27]. On the contrary, low patency of bypass graft is asymptomatic in most cases, despite the fact that previously revascularized segment of the myocardium has no additional perfusion. The CABG surgery also has several aspects that could be improved, including the wider use of arterial shunts, the development of minimally invasive surgical access, the minimization of stroke risk, and the optimization of secondary pharmacological prophylaxis.

Revascularization for patients with peripheral arterial disease and diabetes mellitus

DM is the second most significant risk factor for PAD after smoking, which is present in 20–30% of patients and increases the presence of this pathology by 2–4 times [28, 29]. Patients with DM and PAD have high rate of disease progression, many functional impairments, low quality of life, frequent development of cardiovascular complications and amputations compared with patients with PAD without DM [30–32]. The therapeutic approach to patients with PAD includes: the relief of specific symptoms of any localization, the prevention of PAD relapse and the prevention of consequences associated with atherosclerosis of coronary and cerebral arteries. Revascularization is recommended for patients with severe intermittent claudication and critical limb threatening ischemia. Endovascular intervention is primary method of revascularization in symptomatic PAD, but the difference in outcomes between this procedure and lower-extremity bypass grafting is still an issue of increased concern. The choice of revascularization strategy in patients with PAD depend on the localization, morphology and prevalence of arterial occlusions, that are detailed in the guidelines on the diagnosis and treatment of PAD [10]. The features of revascularization in patients with PAD and DM are not included in the current guidelines due to the lack of studies in this category of patients.

It is worth noting the results of the analysis of 14 012 860 cases from data base of patients who were admitted with PAD and DM (type 1 DM in 5.6% of cases, n= 784.720). Patients with type 1 DM were more likely to have severe chronic limb ischemia (45.2% versus 32.0%), trophic ulcer (25.9% versus 17.7%) or complicated ulcer (16.6% versus 10.5%) of lower extremities ($p<0.001$ compared with patients with type 2 DM). Type 1 DM was independently and significantly associated with large number of amputations (adjusted odds ratio, 1.12 with 95% CI from 1.08 to 1.16, $p<0.001$) [33]. These data require the study of the mechanisms of the observed difference and the development of new approaches to reduce the risk of complications.

In patients with critical limb threatening ischemia and ulcers, surgical or endovascular revascularization is the first-line treatment [34]. To accelerate the process of ulcers healing, negative pressure wound therapy, platelet-rich plasma and other modern wet dressings, systemic anti-inflammatory and antibacterial therapy are used [35].

Revascularization in patients with carotid artery disease and diabetes mellitus

Pharmacological therapy should be recommended for most patients with asymptomatic stenosis (60–99%) of extracranial segments of the carotid arteries and high surgical risk. Carotid endarterectomy (CE) or carotid artery stenting (CAS) are considered if the risk of perioperative stroke / death is<3% and the patient's life expectancy is> 5 years.

CE is recommended for patients with symptomatic 70–99% carotid stenosis; which also should be considered in cases of symptomatic 50–69% carotid stenosis. Due to the lack of scientific data, CAS of the arteries should be additionally investigated in case of recently revealed symptoms of 50–99% carotid stenosis and the presence of concomitant pathology, or unfavorable anatomical factors associated with high risk of CE complications. Revascularization of symptomatic 50–99% carotid stenosis is recommended within 14 days after the onset of symptoms. In each symptomatic case the risk of perioperative stroke / death should be<6% for carotid revascularization. Revascularization is not recommended in patients with carotid stenosis<50% [10].

According to the results of 752 carotid revascularizations (58.2% of CAS and 41.8% of CE), it was found that DM was associated with higher periprocedural risk of stroke or death (3.6% with DM versus 0.6% without DM, p<0.05), transient ischemic attack (1.8% with DM versus 0.2% without DM, p> 0.05) and restenosis (2.7% with DM versus 0.6% without DM, p<0.05). During the 36-month follow-up, there were no significant differences in the incidence of death, stroke, and transient ischemic attack between patients with and without DM in CAS and CE subgroups. Patients with DM showed higher rate of restenosis (estimated risk of restenosis: 21.2% in patients with DM versus 12.5% in patients without DM, p<0.05) [36]. DM is also one of the main risk factors for restenosis after revascularization of the carotid arteries according to other authors [37]. In addition, patients with DM have higher risk of ischemic brain damage during CAS, despite the use of embolic protection devices [38].

Pharmacological treatment for the prevention of atherosclerotic complications in patients with diabetes mellitus

Several lifestyle changes should be recommended in addition to pharmacotherapy, such as smoking cessation, healthy diet, obesity correction and regular exercise.

It is known that adequate treatment of DM is essential for successful revascularization, since preoperative glycosylated hemoglobin level of> 8% and, especially, of> 9% is associated with increased mortality and adverse cardiac events after CABG [39]. In the study by Lee HF et al. (2020), the use of sodium-glucose cotransporter type 2 inhibitors (dapagliflozin, empagliflozin) for the treatment of type 2 DM compared with dipeptidylpeptidase-4 inhibitors reduced the risk of heart failure (RR 0.66 with 95% CI from 0.49 to 0.89, p= 0.0062), lower limb ischemia requiring revascularization (RR 0.73 with 95% CI 0.54 to 0.98, p= 0.0367), amputation (RR 0.43 with 95% CI from 0.30 to 0.62, p<0.0001) and cardiovascular mortality (RR 0.67 with 95% CI from 0.49 to 0.90, p= 0, 0089) [40]. Glucagon-like peptide-1 agonists (dulaglutide, liraglutide, semaglutide) are recommended in patients with type 2 DM with established atherosclerotic CVD as more active agents for the prevention of complications [5]. Large randomized trials on the comparison of sodium-glucose cotransporter type 2 inhibitors and glucagon-like peptide-1 agonists with the assessment of cardiovascular outcomes have not been performed. According to the meta-analysis of 8 studies in patients with type 2 DM (n= 77.242), glucagon-like peptide-1 agonists and sodium-glucose cotransporter type 2 inhibitors both similarly reduced the risk of major cardiovascular complications (RR 0.87 with 95% CI from 0.82 to 0.92 and 0.86 with 95% CI from 0.80 to 0.93, respectively) [41].

The treatment of AH in patients with DM should include an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker with calcium channel blocker and / or a diuretic to achieve target blood pressure level (systolic<130 mmHg with good tolerance, but> 120 mmHg; in patients aged> 65 years — 130–139 mm Hg; diastolic — <80 mm Hg, but>70 mm Hg) [4, 5].

Statins should be used in patients with DM with atherosclerosis in high doses (the target level of low-density lipoproteins with very high cardiovascular risk — <1.4 mmol/L), which reduces the risk of cardiovascular complications, including number after PCI and CABG [4, 5, 42]. However, patients with DM taking statins may have elevated triglyceride levels associated with higher risk of cardiovascular events [43]. In this case, the additional use of ethyl eicosapentaenoic acid significantly reduces the frequency of PCI (RR 0.68 at 95% CI from 0.59 to 0.79, p<0.0001) and CABG (RR 0.61 at 95% CI from 0.45 to 0.81, p= 0.0005) [44].

Antiplatelet therapy with 75–100 mg / day aspirin is recommended in patients with DM for secondary prevention or in patients with high / very high cardiovascular risk for primary prevention. It is recommended to use the P2Y12 receptor antagonists such as ticagrelor or prasugrel for 1 year in combination with aspirin in patients with DM and ACS as well as in patients after PCI or CABG [4, 5]. In patients with stable atherosclerotic vascular disease, including those with DM, the combination of 2.5 mg 2 times / day rivaroxaban and 100 mg / day aspirin, compared with aspirin alone, reduced the risk of MI, stroke and cardiovascular mortality, as well as large amputations [45], indicating the effect of combined antithrombotic therapy.

Conclusion

Modern treatment of patients with DM especially in combination with atherosclerosis, should be performed by endocrinologist and a cardiologist with the involvement of other specialists, if necessary. A team patient-centered approach for the management of such patients will allow to choose and continue the most effective and safe therapy, where revasculariza-

Table. **The choice of preferred method of arterial revascularization and pharmacological treatment that can improve outcomes in patients with DM**

<table>
<tr><th>Cardiovascular disease associated with atherosclerosis</th><th>Primary revascularization method</th><th>Primary pharmacological treatment</th><th>Pharmacological treatment according to indications</th></tr>
<tr><td>ACS</td><td>CABG</td><td rowspan="4">Dulaglutide / liraglutide / semaglutide; dapagliflozin / empagliflozin; statins; aspirin</td><td>P2Y12 receptor blockers</td></tr>
<tr><td>Stable CHD with MVD</td><td>CABG</td><td rowspan="3">Rivaroxaban</td></tr>
<tr><td>ADLE</td><td>Endovascular intervention</td></tr>
<tr><td>Carotid artery stenosis</td><td>catheter endarterectomy</td></tr>
</table>

tion of the coronary and peripheral arteries should have an important place considering indications and contraindications. New pharmacotherapy options for patients with DM and atherosclerotic CVDs can reduce the need for interventional and surgical procedures, as well as improve outcomes after its implementation.

The table summarizes the main ways to improve outcomes of patients with DM and atherosclerotic cardiovascular diseases.

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