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Coronary Revascularization in Patients with Coronary Artery Disease Against the Background of Type II Diabetes Melitus (Review)

Sh. M. Ubaydullaeva[1], B. A. Alyavi[1], N. M. Latipov[1], S. R. Kenjaev[2]

[1]The Republican Specialized Scientific and Practical Medical Centre of Therapy and Medical Rehabilitation, Tashkent, Uzbekistan
[2]The Republican Research Centre of Emergency Medicine, Tashkent, Uzbekistan

Abstract **The aim** of this review was to assimilate current data comparing coronary artery bypass grafting (CABG) and percutaneous coronary interventions (PCI) in patients with type II diabetes mellitus, and to provide a perspective on recent advances in percutaneous interventions as well as optimal treatment options for patients with type II diabetes mellitus. **Background.** Diabetes mellitus accelerates the development of atherosclerosis. Patients with type II diabetes mellitus have higher rates of morbidity and mortality from cardiovascular diseases and undergo a disproportionately higher number of coronary interventions in compare with the general population. Therefore, the correct choice of treatment methods is extremely important. Treatment tactics include medication and interventional approaches, including coronary artery bypass surgery (CABG) and percutaneous coronary interventions (PCI). We conducted a systematic search in PubMed, Web of Science and EMBASE to identify prospective randomized trials comparing the results of CABG and PCI, as well as PCI using stents of different generations used in patients with type II diabetes mellitus. **Conclusions.** Most studies demonstrate the survival advantage of CABG compared with PCI in diabetic patients. However, recent advances in PCI technology may challenge this claim. Improved stent design, the use of special drug-eluting stents, image-guided stent placement, and the use of modern antiplatelet and lipid-lowering therapies continue to improve PCI outcomes.

Keywords Coronary artery disease, CABG, Diabetes mellitus, PCI, Coronary interventions, Atherosclerosis

1. Introduction

The frequency of cardiovascular diseases in patients with type II diabetes mellitus (DM) is higher than the average in the population, and the life prognosis in patients with coronary artery disease (CAD) in combination with DM is worse compared with the prognosis in patients without diabetes. Considering the high prevalence of diabetes among the population and the high mortality of patients with diabetes associated with cardiovascular pathology, it is of interest to study different approaches to the treatment of patients with CAD in combination with diabetes. Along with drug therapy for patients with CAD, including antithrombotic, anti-ischemic, anti-atherosclerotic components, coronary artery bypass grafting, minimally invasive bypass surgery, and endovascular methods (transluminal balloon coronary angioplasty, atherectomy, stenting) are widely used. Coronary balloon angioplasty is an organ-saving, low-traumatic method, feasible for discrete lesions, allowing early activation of patients after the intervention. The main goal of the revascularization performed is very critical in this context - to return the stunned or hibernating myocardium to function [1-3].

Treatment of coronary heart disease against the background of type II diabetes mellitus includes drug treatment of risk factors and, in some cases, the use of interventional strategies. Interventional approaches include percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), while CABG has historically had excellent results. Current data and recommendations lag behind the rapid development of PCI technology, and evaluation of these new systems will inevitably change future treatment paradigms.

The aim of this review was to collect important clinical studies comparing CABG and PCI, as well as comparing different types of stents in type II diabetes, discussing the strengths and weaknesses of various coronary interventions and the latest technological advances to improve interventional outcomes.

Progression of coronary heart disease in type II diabetes mellitus. The pathophysiological environment in diabetes causes a high risk of atherosclerosis and leads to complex lesions of the coronary arteries with lesions of several segments and vessels. The left anterior descending artery (LAD) is more severely affected and the collateral vascular

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network is poorly developed, causing anatomical variants to be at risk for worse outcomes [4-6]. Hyperglycemia leads to the formation of glycosylation end products (AGE), which modify proteins and lipids of the cell surface, causing signal transmission disorders, excessive oxidative stress and a decrease in the extensibility of the vascular wall. Diabetes promotes the activation of protein kinase C (PKC) and the production of diacylglycerin (DAG). PKC/DAG accelerates atherosclerosis by promoting inflammation and recruitment of smooth muscle cells. Activation of PKC also reduces endothelial nitric oxide (NO) production by inhibiting endothelial NO synthase (eNOS) and increases endothelin production, thereby inhibiting vasodilation and increasing oxidative stress [7-9].

Diabetes mellitus also promotes vascular inflammation by increasing the expression of proinflammatory genes such as nuclear factor-κB (NF-κB), which stimulates the recruitment of leukocytes and smooth muscle and thereby increasing lipid uptake by macrophages. Diabetes accelerates vascular remodeling by activating matrix metalloproteinases (MMP-1 and 2), which leads to vulnerability of plaque physiology and increases the risk of thrombosis and rupture. Diabetes coexists with obesity and hypertension as part of the metabolic syndrome, both of which increase the risk of coronary artery disease. As it is known, the metabolism of lipids changes in diabetes. Hypertriglyceridemia is the most common dyslipidemia associated with diabetes and has an atherogenic effect indirectly through the metabolism of triglyceride-rich lipoproteins (TGRL). Smaller particles of low-density lipoprotein cholesterol (LDL-C) are more easily oxidized in diabetes, which increases their atherosclerotic potential, allowing for easier absorption into vessel walls [10-11]. HDL cholesterol and apolipoprotein A1 levels decrease in diabetes. Diabetes mellitus increases platelet activity. Hyperglycemia promotes the expression of thromboxane (TxA2), p-glycoprotein, and von Willebrand factor (vWF), which are activators of platelet adhesion and activity. Diabetes worsens platelet sensitivity to NO and prostaglandin I2 (PGI2), agents that inhibit platelet activation, modifies the profile of platelet receptors, reducing the efficiency of antiplatelet drugs [12-17].

Intravascular imaging and histopathology have demonstrated decreased fibrous cap thickness, increased lipid, calcium, and inflammatory load in atherosclerotic plaques in patients with diabetes, histological variants that portend a higher risk of adverse events in these plaques [18-19].

Approaches to the treatment of coronary heart disease in diabetes mellitus. Optimal drug therapy (ODT) is the cornerstone of stable management of coronary heart disease. Medical therapies based on clinical guidelines have demonstrated similar results compared to interventional strategies in many large-scale researches, including the COURAGE and ISCHEMIA studies. ODT is also the initial therapy for coronary heart disease in diabetes. The BARI-2D and subanalysis of the COURAGE study did not reveal significant benefits of adding interventions in compared with ODT (except for a decrease in cardiovascular events in the CABG + ODT cohort in BARI-2D). The modern arsenal of antidiabetic agents includes sodium-glucose transporter-2 inhibitors (SGLT-2) and glucagon-like peptide agonists (GLP-1), which provide a significant improvement in combined cardiovascular outcomes in patients with diabetes [20-25].

Antiplatelet therapy is another key component of the treatment of coronary heart disease, and the efficiency of antiplatelet agents in diabetes differs compared with nondiabetic patients requiring careful drug selection. Optimal treatment of hyperlipidemia and hypertension is essential to reduce the risk of cardiovascular events in diabetes mellitus, especially after PCI [26].

To determine the risk and decide on an intervention, a comprehensive evaluation of coronary heart disease in diabetes using non-invasive testing is necessary. It can be done in the form of dynamic (radionuclide, electrocardiography, stress testing based on echocardiography) or anatomical assessment (coronary computed tomography angiography (CCTA) [27-30]. Appropriate selection of patients and procedures depends on test results and target outcomes. Our review will focus on discussing aspects of interventional treatment of diabetes mellitus that can be used after proper clinical evaluation.

Traditional approaches to revascularization. According to Camp, House JA, Messenger JC, et al., patients with diabetes make up one third of all percutaneous interventions performed. The incidence of incomplete revascularization and complications from these procedures is much higher in diabetic patients in compare with the general population. There are two main interventional approaches to treatment - Coronary artery bypass grafting (CABG) and Percutaneous coronary intervention (PCI). The treatment of CAD and its results have changed over the years, largely depending on various clinical factors and technological advances [31-33].

Coronary artery bypass grafting (CABG) involves surgical transposition of autologous arteries/veins to bypass obstruction of the coronary arteries and provide coronary blood flow to the underlying myocardium.

Percutaneous coronary intervention (PCI) is a minimally invasive approach that uses ballooning/stenting to open occluded coronary lesions. Early percutaneous interventions included balloon dilation angioplasty. PCI currently includes stenting of lesions, which prevents the vessel from rolling back and promises long-term patency of the vessels.

Comparative data on PCI and CABG. Early studies evaluated CABG and PCI with balloon angioplasty. In the diabetic cohort in the CABRI (1994) study (n = 125), a statistically insignificant higher mortality rate from all causes was observed in patients undergoing angioplasty. The subgroup of diabetics in the BARI (1996) study demonstrated significantly better 5-year survival in the CABG group (80.3%) compared with the balloon angioplasty group (60.5%) (p=0.003) and CABG favourable outcomes occurred even after 7 years [34-35]. The superior cardiovascular outcomes of CABG compared with PCI for diabetes are primarily due to higher rates of complete revascularization and preservation of the natural endothelial response in CABG compared with maladaptive endothelial pathophysiology in the stented vessel [36-38]. This benefit is important for patients with diabetes due to the severity of the disease.

CABG is an "endogenous stent" that bypasses several stenosed areas, which leads to more complete revascularization and greater protection against future thrombosis compared to stents that revascularize individual foci. Autologous vessels are less immunogenic and thrombogenic than stents and provide a more physiological environment. Subcutaneous vein grafts (SVGs) were initially used and are increasingly being replaced by arterial conduits due to higher rates of long-term vein graft failure due to vascular remodeling [39,40]. Data from the Coronary Artery Surgery Study (CASS) and other large-scale researches have demonstrated better long-term patency of arteries over vein grafts. Internal mammary artery (IMA) grafts in particular preserved endothelial functions such as vasodilation and had higher blood flow reserve due to higher compliance [41-46]. Non-adherence to antiplatelet therapy is not fatal in CABG, as it can be in PCI.

Restenosis and thrombosis are the main pathogenic mechanisms which lead to worse results in vessels treated with PCI, and they are aggravated in diabetes. Restenosis involves narrowing of stented areas due to fibroinflammatory deposits, starting with an initial thrombogenic reaction, followed by migration of inflammatory cells and, finally, hyperplasia and remodeling of intima. Stents are foreign bodies and, therefore, more thrombogenic, which leads to an increased risk of early (<1 month) or late (1 month-1 year) stent thrombosis. Delayed healing and impaired endothelization of the stented area play a role in this process [47-49]. Multivessel disease, which requires the installation of multiple stents, increases these risks. However, the frequency of interventions is disproportionately biased towards the use of PCI [50,51], despite the scientifically proven superiority of CABG. Minimal invasiveness and a shorter stay in a hospital after the procedure make PCI a very attractive approach for patients. CABG entails a higher risk of deep tissue infection due to open sternotomy and a higher risk of stroke due to the use of cardiopulmonary bypass [52]. The "test and treat" approach, including the conversion of diagnostic catheterization into a PCI procedure, might be another possible reason for the increased use of PCI [53]. The benefits of new PCI technologies are sometimes applied on a guesswork basis, as rapidly changing advances result in a paucity of prospective data.

An individual evaluation based on risk factors is necessary to stratify patients in order to choose the optimal interventional approach. A cardiac team consisting primarily of cardiologists and cardiothoracic surgeons helps for achieving interdisciplinary consensus and is believed to lead to improved outcomes. Evaluation systems such as EuroSCORE and SYNTAX also help to make decisions in favor of an interventional treatment method. EuroSCORE I and II predict mortality after cardiac surgery [55-57]. However, these indicators have not been sufficiently tested in the population of the patients with diabetes. The SYNTAX score evaluates the severity and complexity of CAD [58]. Higher SYNTAX scores are associated with a greater advantage of CABG in compare with PCI. A posteriori analysis of SYNTAX scores in diabetic patients treated in the FREEDOM study noted a correlation of SYNTAX scores with PCI results, but did not reveal any benefit from calculating SYNTAX scores when changing recommendations from CABG to PCI [59].

Left ventricular systolic dysfunction (LVSD), the main complication of coronary artery disease, is considered a risk factor for such a serious surgical intervention as CABG. However, the data from the STICH study showed that the addition of CABG to drug therapy helped to reduce significantly the incidence of hospitalization for cardiovascular diseases and cardiovascular mortality compared with drug therapy alone in patients with LVSD. A 12-year follow-up retrospective study demonstrated a significant improvement in MACCE and mortality from cardiovascular diseases, total mortality in CABG compared with PCI in patients with diabetes and LVSD (ejection fraction<35%). Further prospective studies are needed to clarify the situation regarding the use of CABG in this population group, which has a higher surgical risk, but may benefit more from the bypass option in the long term perspective [60-65]. Lesion of the left main coronary artery (LMCAD) in CAD portends a high risk of future complications and worse outcomes, and in diabetic patients it is usually treated using CABG. Comparative data on cases of isolated coronary artery disease of the left main coronary artery (LMCAD) in diabetes have also been updated: MAIN-COMPARE and EXCEL data show similar cardiovascular outcomes in PCI compared with CABG in diabetes. Chronic total occlusions (CTO) (>3 months) of the coronary arteries (TIMI 0 flow) are more common in patients with diabetes. CTO is mainly treated with anginal drug therapy and CABG. CTO PCI is considered high risk and is performed in specialized centers with the necessary equipment and an experienced cardiac surgery team. Patients with single-vessel CTO and those who have previously had CABG are probable candidates for CTO PCI. Another clinical situation for the preferred use of PCI in diabetic patients is the worsening of CAD after CABG. Repeated surgery in such cases is associated with a high risk of mortality and PCI is a reasonable option [63-69].

Recent advances in PCI and CABG technologies. Interventional cardiology is evolving at a breakneck pace. Significant progress has been made in the development of new generation drug-eluting stents (DES), which have a thinner structure, biosimilar design, and better and longer-lasting drug action and delivery. Bioresorbable DES/frameworks (BR-DES/BRS) are advanced generation stents with a bioresorbable design and theoretically with a lower risk of thrombosis. However, early BRS stents demonstrated a higher incidence of very late thrombosis in the BRS group, which led to their withdrawal from the market. According to House M, Buiten R, the results of the new BRS/BD-DES look promising, and long-term data on their application are expected [70-79].

Imaging strategies, including fractional flow reserve (FFR), optical coherence tomography (OCT), and instantaneous wave-free ratio (iFR), are used to restratify intermediate lesion severity in angiographic studies, resulting in significant modification of the treatment plan. However, the benefit in diabetes has not been proven [80-82].

Improvement of PCI outcomes through proper stent selection, placement and technique. Intravascular ultrasound (IVUS) and optical coherence tomography (OCT)-guided stent placement techniques are used to determine the characteristics and severity of coronary lesions. These intracoronary imaging techniques help to choose the right stent, length, placement, and technique to refine the results of minimizing risk after stenting. Targeted interventions for plaques with high-risk characteristics diagnosed with OCT/IVUS allow the selective use of PCI in the most severe areas and narrow the therapeutic difference between PCI and CABG in patients with type II diabetes [83-86].

For CABG, revascularization using bilateral IMA has shown mixed results in the general population, with improved mortality in large observational studies and meta-analyses, which was countered by the results of the large ART trial (2019), which showed no significant benefit on 1-year mortality. Off-pump CABG and minimally invasive CABG did not have a significant effect on CABG outcomes [87-92].

Hybrid coronary revascularization (HCR) attempts to use the left internal mammary artery for anatomical bypass surgery of the anterior interventricular artery (ensuring maximum survival) in combination with percutaneous coronary intervention on small vessels which are not the anterior interventricular artery. This approach is especially useful when bypass surgery of certain vessels or advanced thoracic access is not possible, or if second arterial grafts are not available. Existing data indicate similar results with traditional coronary bypass surgery. This option is not a common practice, and the lack of a major prospective analysis limits its widespread use [93-95].

2. Conclusions

Coronary artery disease and diabetes mellitus are epidemics of the modern era and are closely interrelated. Typical approaches and outcomes of CAD therapy in the general population cannot be extrapolated to diabetics due to their significantly increased risk of CAD. Current data indicate a very strong advantage of CABG over PCI in such type of patients, both in terms of recurrent events and mortality. Taking into account current advances in PCI technology and the latest antidiabetic and antiplatelet drugs, we expect to improve results in the future with minimally invasive methods. Risk stratification and an open discussion with the patient about the risks and benefits of each procedure are important. The role of the primary care physician is vital for secondary prevention and adherence to the treatment regimen, which is important for the prevention of thrombosis. Despite the enormous advances in PCI technology, however, from an evidence point of view, the superiority of CABG is still kept.

Conflict of Interests

The authors declare no conflict of interest.

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