DOI: 10.20514/2226-6704-2023-13-2-97-109
УДК 616.12-005.4-036.12+616.379-008.61-08
EDN: ISYXZU

Е.В. Щукина*, О.А. Приколота, В.А. Багрий, А.Ю. Андрусяк, Г.С. Рыбалко, Ю.Б. Шестерина, Е.А. Стефано

Государственная образовательная организация высшего профессионального образования «Донецкий национальный медицинский Университет им. М. Горького», Донецк, ДНР

ЛЕЧЕНИЕ ПАЦИЕНТОВ С ХРОНИЧЕСКОЙ ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА И САХАРНЫМ ДИАБЕТОМ 2 ТИПА

E.V. Shchukina*, O.A. Prikolota, V.A. Bagrij, A.Ju. Andrusjak, G.S.Rybalko, Yu.B. Shesterina, E.A. Stefano

State Educational Institution of Higher Professional Education «M. Gorky Donetsk National Medical University», Donetsk, DPR

Treatment of Patients Chronic Coronary Heart Disease and Type 2 Diabetes Mellitus

Резюме

Сочетание хронической ишемической болезни сердца и сахарного диабета 2 типа у пациента имеет высокую медицинскую значимость и привлекает к себе растущее внимание мирового врачебного сообщества. Серьезные изменения, произошедшие в лечебной тактике у пациентов, имеющих сочетание ишемической болезни сердца и сахарного диабета 2 типа, требуют пристального внимания. Современные подходы к терапии этой группы пациентов включают в себя направления, улучшающие сердечно-сосудистый прогноз (изменение образа жизни, прием антитромботических препаратов, антигипертензивной терапии, гиполипидемических средств — статинов и нестатиновых гиполипидемических препаратов (которые показаны пациентам, тяжело переносящим лечение статинами), сахароснижающих препаратов), а также внимательное ведение синдрома стабильной стенокардии (прием антиангинальных средств, оценка возможностей реваскуляризации). Новая линия сахароснижающих препаратов обладает высокими кардиопротекторными свойствами, снижает интенсивность поражения сосудистого русла (вазопротекция), оказывает ренопротекцию. Стратегия выбора сахароснижающих препаратов претерпела ряд изменений и в данный момент обозначается, как «дифференцированная», что подразумевает необходимость выбора препарата с наибольшими органопротективными свойствами. Достижение целевых уровней гликированного гемоглобина (HbA_{1C}) в границах 7,0-8,0 % ассоциировано с наименьшим уровнем смертности пациентов. Кроме того, пациентам с сахарным диабетом 2 типа, в особенности имеющим ишемическую болезнь сердца, рекомендовано свести к минимуму эпизоды развития гипогликемических состояний. Данное сообщение ставит перед собой задачу подробно обсудить основные подходы к ведению пациентов с ишемической болезнью сердца и сахарным диабетом 2 типа, а также подходы к улучшению сердечно-сосудистого прогноза.

Ключевые слова: *ишемическая болезнь сердца, сахарный диабет 2 типа, сердечно-сосудистые заболевания, сердечно-сосудистый прогноз*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 27.05.2022 г.
Принята к публикации 09.12.2022 г.

Для цитирования: Щукина Е.В., Приколота О.А., Багрий В.А. и др. ЛЕЧЕНИЕ ПАЦИЕНТОВ С ХРОНИЧЕСКОЙ ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА И САХАРНЫМ ДИАБЕТОМ 2 ТИПА. Архивъ внутренней медицины. 2023; 13(2): 97-109. DOI: 10.20514/2226-6704-2023-13-2-97-109. EDN: ISYXZU

*Контакты: Елена Викторовна Щукина, e-mail: schukina.elena@mail.ru
*Contacts: Elena V. Shchukina, e-mail: schukina.elena@mail.ru
ORCID ID: https://orcid.org/0000-0002-9022-6155

Abstract

The combination of chronic coronary heart disease and type 2 diabetes mellitus in a patient has high medical importance, because relevance of the problem increases every year. Modern requirements for the provision of high-quality medical care to patients with combined pathology require attentive assessment: we can't deny the pathophysiological relationship of both diseases. Serious changes that occurred in the treatment tactics in relation to such patients require close attention of the medical community. Modern approaches of the therapy of this group of patients include treatment directions that improve the cardiovascular prognosis (lifestyle changes, anti-platelet therapy, antihypertensive therapy, statins and nonstatin lipid-lowering agents, which are indicated for patients who are difficult to tolerate statin treatment, glucose-lowering drugs), as well as careful management of stable angina syndrome (using of antianginal drugs, assessing the possibilities of revascularization). The therapeutic tactics of the new revision offers promising perspective regimens for taking antiplatelet therapy, lipid-lowering drugs. The new line of glucose-lowering drugs has high cardioprotective properties, reduces the intensity of vascular lesions (vasoprotection), and has renoprotective properties. The strategy of choosing glucose-lowering drugs has also undergone some changes: at the moment it is designated as «differentiated», which implies choosing a drug with the highest organoprotective properties. Achievement of target HbA1C levels in the range of 7.0-8.0 % is associated with the lowest patient mortality rate. In addition, to patients with type 2 diabetes mellitus, especially group with coronary heart disease, advised to minimize episodes of hypoglycemic conditions. Aim of this statement is to discuss in detail progressive approaches in the treatment of patients with chronic coronary heart disease and type 2 diabetes mellitus.

Key words: *coronary heart disease, type 2 diabetes mellitus, cardiovascular diseases, cardiovascular prognosis*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 27.05.2022
Accepted for publication on 09.12.2022

For citation: Shchukina E.V., Prikolota O.A., Bagriy V.A. et al. Treatment of Patients Chronic Coronary Heart Disease and Type 2 Diabetes Mellitus. The Russian Archives of Internal Medicine. 2023; 13(2): 97-109. DOI: 10.20514/2226-6704-2023-13-2-97-109. EDN: ISYXZU

AH — arterial hypertension, BP — blood pressure, CABG — coronary artery bypass graft, ACE — angiotensin converting enzyme, GLP-1-RA — glucagon-like peptide-1 receptor agonist, ASA — acetylsalicylic acid, CCB — calcium channel-blocking agent, DAPT — dual antiplatelet therapy, DNP — diabetic nephropathy, CHD — coronary heart disease, DPP-4i — dipeptidyl peptidase-4 inhibitor, MI — myocardial infarction, SGLT-2i — sodium-glucose linked transporter-2 inhibitor, CA — coronary artery, LV — left ventricle, HDL — high density lipoproteins, LDL — low density lipoproteins, OMT — optimal medical therapy, T2DM — type 2 diabetes mellitus, HF — heart failure, TG — triglycerides, EF — ejection fraction, PCI — percutaneous coronary intervention, HbA_{1C} — glycated hemoglobin, β-ABs — β-adrenoblockers, ω3-PUFA — ω3-polyunsaturated fatty acids

Introduction

The issue of concomitant coronary heart disease (CHD) and type 2 diabetes mellitus (T2DM) is of high social significance, attracting increasing attention of the global medical community. In spite of existing separate Guidelines for each of these conditions, which are subject to regular update, in 2020, the experts of the American Heart Association (AHA) published a scientific statement, defining the principles of treatment of patients with stable CHD and T2DM. Due to close pathophysiological relationship between CHD and diabetes mellitus, some experts raise the question about the inevitability of coronary involvement in T2DM. In recent years, there have been major changes in the views on the treatment strategy for this patient group; additional promising administration schedules have been proposed for antithrombotic and lipid-lowering agents; glucose-lowering agents with persuasive cardio-, vasoprotective and renoprotective effects have emerged. At the same time, in many cases, the actual state of medical care for patients with CHD and diabetes mellitus does not meet modern requirements. For example, according to the data from the latest EUROASPIRE V registry, a large proportion of these patients do not receive necessary cardioprotective agents, and the frequency of reaching target blood pressure (BP), cholesterol (C), and glycated hemoglobin (HbA_{1C}) is "far from the desired" [1].

This publication is aimed at discussing modern approaches to the treatment of patients with chronic CHD and T2DM. When considering these issues, the authors used both the AHA scientific statement mentioned above and other modern guidelines [1, 2].

Approaches to improve cardiovascular prognosis

Change in lifestyle

Lifestyle changes, including smoking cessation, rational diet, slimming, control of psycho-emotional stress, and moderate physical activity, are cornerstones for the treatment of patients with both T2DM and CHD.

Smoking cessation is an urgent measure for all patients with T2DM, regardless of CHD presence. Diverse adverse cardiovascular effects of smoking have been clearly demonstrated. In patients after myocardial infarction (MI), smoking is associated with a significant (51 %) increase in the risk of recurrent MI [3]. Smoking cessation significantly reduces coronary risk, reaching the nonsmoker levels–about three years after cessation.

Favorable effects of smoking cessation do not depend on the presence of T2DM. Smoking cessation can be accompanied by a moderate weight gain (about 5 kg), which can be considered a problem for some patients. It has been shown that such increase in body weight, even in persons with T2DM and obesity, does not affect the extent of cardiovascular risk reduction achieved by smoking cessation [3].

A rational, balanced, and healthy diet is considered as "the cheapest and natural" approach to reducing the clinical manifestations and the rate of T2DM progression and its microvascular and macrovascular complications. When dietary advice is implemented in practice, the extent of HbA_{1C} reduction is similar to or even greater than that achieved on medical treatment; adherence to a healthy diet significantly reduces the need for expensive drug products. In the primary prevention trial PREDIMED (7447 patients at high cardiovascular risk, of whom 3614 had T2DM), the use of the Mediterranean diet led to a 30 % reduction in the risk of composite endpoint, including cardiovascular death, MI, and stroke; this beneficial effect did not depend on the presence of diabetes mellitus [4]. The choice of food products may be based on the bread unit count, which is widely presented in special tables. It is considered necessary that the diet of patients with T2DM should contain an increased quantity of vegetables and fruit (primarily non-starchy), dietary fiber, legumes, vegetable proteins, unsaturated fats, and nuts, while reducing the consumption of processed meat products (sausages, etc.). It is recommended that the use of refined carbohydrates and sweet drinks should be minimized. Practical implementation of the developed dietary recommendations is a long and complicated process. In case of patient adherence, the change in food preferences may take at least 2–8 months. To enhance the chances of success, the given advice should be flexible; explanations should be easy to understand, and the willingness to repeat attempts should be guaranteed. The physician's time, personal involvement, and sympathy to the patient are essential conditions for dietary plan implementation [4].

An important component of the nonmedical advice for many patients with T2DM and CHD (especially those with arterial hypertension [AH] and/or diabetic nephropathy [DNP]) is the reduced use of kitchen salt (<5 g of sodium chloride a day). This amount of salt is fairly well tolerated, has no adverse biological effects, helps reduce BP, reduces the risk of cardiovascular complications, slows the rate of renal involvement progression, increases organic protective effect of renin-angiotensin-aldosterone system blockers, and increases the effect of diuretic therapy. It is important to explain to patients that by observing dietary salt restriction, the individual taste perception threshold also decreases within 4 to 6 weeks, and, subsequently, a low-salt diet becomes quite comfortable [5].

Control of psycho-emotional stress and sleep disorders Epidemiological data (REGARDS, ADDITION trials) are suggestive of a distinct relationship between macrovascular complication of T2DM (including MI, stroke, need for revascularization, and limb amputation) with signs of depression and psychosocial distress. The mechanisms of this association are still unclear; the effect of correction of these disorders on the course of CHD and T2DM also requires clarification.

Sleep disorders, which are often closely associated with obesity, have been identified as an adverse factor to be controlled in diabetic patients. Their association with sympathetic nervous system hyperactivity, pro-inflammatory reactions, and endothelial dysfunction has been demonstrated. Correction of obstructive sleep apnea has a favorable impact on the BP levels and a number of positive cardiometabolic effects. Other sleep problems, including its insufficient duration, can be accompanied by adverse effects on the lipid profile, insulin resistance, and vegetative balance, which is very important for patients with concomitant T2DM and CHD [6].

Regular graduated exercise in patients with T2DM helps reduce the levels of blood sugar, BP and inflammatory markers, normalize body weight, improve lipid profile parameters and muscle strength, reduce the tendency to depression, improve quality of life, and have a favorable effect on the prognosis. A lot of patients and diabetes mellitus and CHD are prone to sedentary lifestyle. The current guidelines on the management of patients with concomitant T2DM and stable CHD include (1) while being awake, a prolonged resting state should be interrupted every 30 minutes with light physical activity and (2) cumulatively, maintaining at least 150 minutes of moderate or significant physical activity per week as a necessary element of treatment strategy [7, 8].

Slimming is an important component of T2DM and CHD treatment in obese patients. The main approaches include a low-calorie diet (usually 1200–1500 kcal/day for women and 1500–1800 kcal/day for men, with an energy deficit of about 500 kcal/day), increased physical activity, and changes in eating habits and behavior. During the controlled slimming, the initial goal is the loss of 5 %–10 % of body weight over 6 months. In rare cases, when these approaches appear to be ineffective, medical therapy and bariatric surgery (usually, in patients with body mass index ≥35–40 kg/m^2) [8, 9].

Antithrombotic agents

Currently, T2DM is considered as generalized hypercoagulable state. Hyperglycemia and hyperinsulinemia, which are typical of diabetes mellitus, have adverse effects on the vascular endothelium, interrupt atheroprotective NO-dependent regulatory mechanisms, contribute to the formation of proinflammatory and vasoconstrictor effects, cumulatively favoring atherothrombosis. T2DM is associated with a number of platelet receptor apparatus defects, dysregulation of their adhesion functions, activation and aggregation, increased destruction and decreased duration of platelet existence, a relative increase in the number of large immature platelet forms in circulation. Expectations regarding blocking of prothrombotic effects of DM are related to the evolution of antithrombotic agents, emergence of their more powerful representatives, and introduction of more advanced therapeutic regimens [10].

Acetylsalicylic acid (ASA) and clopidogrel

Treatment with antiplatelet agents is a fundamentally important component of secondary prevention in patients with T2DM; by reducing the thrombogenic potential, they reduce cardiovascular risk. DM-related abnormalities of the platelet receptor apparatus can lead to a decreased response to treatment with ASA (75–100 mg/day) and dual antiplatelet therapy (DAPT) with clopidogrel (75 mg/day), which is even more pronounced in concomitant DNP with impaired renal function. Some authors suggest increasing in frequency of administration and/or the dose of antiplatelet agents (e.g., ASA 75 mg twice daily) as one of the measures to overcome this effect; however, the safety of such alternative regimens needs to be confirmed. In some patients with T2DM and stable CHD (in the absence of stenting or MI within the last year), administration of clopidogrel alone in the standard dose instead of ASA may be justified (in the randomized controlled trial (RCT) CAPRIE, clopidogrel was significantly superior to ASA, reducing the risk of ischemic complications without a significant increase in bleeding risk: as in the whole of 19,185 patients with an increased cardiovascular risk as in the subgroup of 3866 patients with diabetes mellitus). Another strategy variant, which may be considered for patients with T2DM and chronic CHD, is the longer-than-usual DAPT (ASA in combination with clopidogrel) [10]. AHA experts consider it possible to recommend this approach to patients at very high cardiovascular risk (e.g., with prior MI, of younger age, smokers), balancing the risk of ischemia and bleeding. To facilitate decision-making, the calculator proposed by R.W. Yeh et al. can be used: (1) 1 point for current cigarette smoker, for diabetes mellitus, for current MI, for prior MI or coronary stenting, for paclitaxel-eluting stent, for stent diameter <3 mm; (2) 2 points for clinical manifestations of heart failure or left ventricular (LV) ejection fraction (EF) <30 %, for vein graft stent; (3) 0 points for age <65 years, 1 point for age 65–74 years, 2 points for age ≥75 years; (4) consideration of the total score: the score of ≥2 points are in favor of long-term use of DAPT [10].

Table. *Calculator ischemia-bleeding risk balance for deciding on long-term dual antiplatelet therapy (adapted by R.W. Yeh et al.)*

Parameters	Score
Smoker	1
Diabetes mellitus	1
Myocardial infarction	1
Post myocardial infarction or coronary stents	1
Paclitaxel-eluting stents	1
Stents diameter <3 mm	1
Clinical manifestations of heart failure	2
Ejection fraction of left ventricular <30 %	2
Stenting of venous shunt	2
Age	
– <65 years	0
– 65-74 years	1
– ≥75 years	2

Note: The presence of ≥2 points indicate in favor of long-term use of DATT

Ticagrelor

The possibility of using this drug product has been expanded based on the data from the large THEMIS RCT presented in 2019. In the trial, the efficacy of ASA alone was compared to a combination of ASA and ticagrelor (60 mg twice daily) in 19,271 patients with T2DM and CHD but without history of MI or stroke. Over 40 months of follow-up, the balance between decreased cardiovascular risk and increased bleeding risk was favorable only for a predetermined group of patients who had previously undergone coronary stenting procedures. It is this category of patients that may benefit from this treatment strategy, provided the risk of bleeding is low [11].

Rivaroxaban

Another opportunity for secondary prophylaxis in persons with T2DM and chronic CHD, in the absence of high risk of bleeding, could be a combination of ASA with a low dose of a new oral anticoagulant: rivaroxaban, an inhibitor of coagulation factor Xa. It is ¼ of the dose that is routinely used for antithrombotic prophylaxis in atrial fibrillation. In a large-scale COMPASS RCT (27,395 patients with chronic CHD not requiring standard DAPT), treatment with ASA in combination with rivaroxaban 2.5 mg twice daily significantly reduced the risk of cardiovascular complications compared to ASA, at the cost of increased risk of nonfatal bleeding. A favorable effect on the cardiovascular prognosis in patients

with T2DM was less pronounced than in patients without DM [12].

Experts of the European Society of Cardiology (ESC) classify all variants of long-term treatment with ASA in combination with other antithrombotic agents as IIa/A and IIb/A at high and moderate levels of cardiovascular risk, respectively, and in the absence of a high risk of bleeding, reserving this approach mainly for postinfarction patients who have already been receiving DAPT for at least 1 year [9].

Platelet function assay Despite the initial enthusiasm concerning the possibility of improving approaches to the choice of antithrombotic strategy in patients with chronic CHD using the evaluation of platelet function, serious RCTs have not been able to confirm these expectations yet [6].

Antihypertensive therapy

The prevalence of arterial hypertension (AH) in patients with T2DM is twice as high as that in the general population. Not less than 70 %–80 % of patients with diabetes mellitus are reported to have AH. Arterial hypertension in T2DM patients is associated with an additional increase in the risk of MI, stroke, and overall mortality. Epidemiological studies demonstrate a steady increase in the incidence of microvascular and macrovascular events in patients with diabetes mellitus with increasing levels of systolic BP above 115 mm Hg [13].

Target blood pressure levels

The issue of BP levels that are considered desirable to provide organ protection and improve prognosis in individuals with AH both in general and in certain categories of patients (the elderly, with diabetes mellitus, with chronic CHD, etc.) has long remained debatable, which created some confusion in the target BP values recommended by different medical associations. This was due to the fact that large RCTs and registries demonstrated contradictory data on the effects of more intensive BP lowering: either negative (INVEST, CLARIFY, ONTARGET, TRANSCEND, ACCORD) or positive (SPRINT). Currently, both Russian experts and leading world communities (American Heart Association, European Society of Cardiology, International Society of Hypertension) share opinion that the most suitable BP levels for the majority of patients with T2DM and chronic CHD may be 120–129 mm Hg (130–139 mm Hg for the age >65 years) systolic and 70–79 mm Hg diastolic [14].

Choice of antihypertensive agents

Angiotensin-converting enzyme inhibitors (ACE) and sartans have traditionally been recognized as the main variants of AH control in patients with diabetes mellitus and CHD, and to improve cardiovascular prognosis (HOPE, EUROPA, VALIANT and other RCTs and their subanalysis) and slow the progression of decline in kidney function. Beneficial effects of these classes of drug products on prognosis are particularly pronounced in postinfarction patients and in those with impaired left ventricular systolic function. Since the vast majority (up to 70 %) of patients with T2DM and AH required >1 therapy, the issue of adequate combination selection is of special importance. It is considered that the most acceptable addition to ACEs and sartans would be dihydropyridine calcium channel blockers (CCBs) and thiazide-like diuretics (indapamide, chlorthalidone). The opinion on thiazide diuretics is less conclusive: their adverse effect on insulin sensitivity, insulin secretion and ability to worsen glycemic control is well known. However, taking into account beneficial effect on cardiovascular prognosis, in serious RCTs (ALLHAT), their use is considered possible [14]. In recent years, there have been active discussions on the possibility of using mineralocorticoid receptor antagonists (spironolactone, eplerenone), which are quite effective in patients with resistant AH and can improve cardiovascular prognosis in patients with impaired LV systolic function. β-adrenoblockers (β-ABs) are mainly reserved for diabetic patients with clinical manifestations of angina, LV EF <40 %, postinfarction patients, and those with cardiac rhythm disturbances. Among the drug products of this class, the preference is given to medications with vasodilating properties (carvedilol, nebivolol), the metabolic side effects of which are less pronounced. The combined hypotensive therapy for T2DM and chronic CHD can also include (if necessary) centrally acting agents (moxonidine and urapidil), α-adrenoblockers (doxazosin), and long-acting nitrates [14, 15].

Lipid-lowering agents

Proatherogenic lipid changes associated with T2DM largely contribute to increased cardiovascular risk. The most typical of them are increased levels of triglycerides (TG), small large particles of low-density lipoprotein cholesterol (LDL-C), apolipoprotein C-III, lipoprotein Lp(a), and decreased levels of high-density lipoprotein (HDL) cholesterol. Persistent hypertriglyceridemia and hyperglycemia contribute to oxidation and glycation of LDL-C particles, thus increasing their atherogenicity. The listed lipid shifts contribute to the formation and progression of endothelial dysfunction, promote proinflammatory and prothrombotic effects, accelerate the development of atherosclerotic vascular disorders. The important role of lipid disorders in prognosis worsening in patients with T2DM is evidenced by data from serious RCTs on a pronounced reduction in the cardiovascular risk on

treatment with medications affecting dyslipidemia activity. In 2020, data from a meta-analysis of 52 RCTs on the assessment of leading lipid-lowering agents: statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 enzyme (PCSK9) inhibitors were published; the analysis included only studies with ≥1000 patient-years; a total of 327,037 patients were included in the analysis. A decrease in LDL-C by 1 mmol/L was shown to be associated with a reduction in the risk of cardiovascular events by 19 %; this effect did not depend on the baseline level of LDL-C (including the baseline levels of 2.0 mmol/L), the used class of lipid-lowering agents, presence of diabetes mellitus or chronic kidney disease [16, 17].

Target levels of LDL-C

When using lipid-lowering agents, it is advisable to strive for achieving target LDL-C levels. According to the European Society of Cardiology experts, for patients with chronic CHD and T2DM, the target levels are (1) <1.8 mmol/L or a 50 % reduction from baseline for high-risk patients; (2) <1.4 mmol/L or a 50 % reduction from baseline for very high-risk patients; (3) and <1.0 mmol/L for patients who have had ≥2 cases of cardiovascular events over the last 2 years [18].

Statins

The use of statins in addition to lifestyle changes play an important role in the primary and secondary prophylaxis of CHD in patients with T2DM. Compared to individuals without diabetes mellitus, in patients with T2DM, the use of statins leads to similar lipid-lowering effects and an equal (or even greater) positive effect on the cardiovascular prognosis in patients with T2DM (RCTs HPS, TNT, JUPITER, etc.).

For patients with chronic CHD and T2DM, current guidelines recommend the choice of high-intensity statin therapy (atorvastatin 40–80 mg/day or rosuvastatin 20–40 mg/day, these doses provide a reduction of LDL-C by ≥50 % versus baseline), and if there are factors limiting their use, such as age >75 years, the use of moderate-dose statins is recommended. It should be noted that if muscle side effects of statins develop, their use in very low doses (less than the standard minimum, e.g., atorvastatin 5 mg every other day) is considered possible, recognizing that statins can have a certain degree of organ protection [19].

Several RCTs and their meta-analyses have demonstrated that statins are associated with a small but statistically significant increase in the risk of T2DM. The level of this risk is lower than that associated with the use of thiazide diuretics and non-vasodilating β-ABs. However, it is most important that the cardiovascular protective effects of statins significantly outweigh the increased risk of diabetes mellitus associated with their use. It has been demonstrated that one additional case of T2DM can develop when treating 255 people with statins for 4 years. Over this time, 5.4 cases of cardiovascular events can be prevented. The analysis that included 9 RCTs (a total of 9696 patients) has shown that in patients who already have diabetes mellitus, an increase in the levels of HbA_{1C} associated with the use of statins is rather moderate and amounts to 0.12 % over 3.6 years. Therefore, it is important that physicians understand and convince their patients that, in spite of a slight increase in glycemic levels that accompanies administration of statins, the risk/benefit ratio for this group of drug products clearly favors their use in patients with T2DM (and its risk factors) in combination with CHD [20, 21].

Non-statin lipid-lowering agents

Although statins play a leading role in the secondary prophylaxis in patients with T2DM and CHD, some patients do not tolerate high doses due to side effects or fail to achieve the desired levels of LDL-C necessary to reduce the cardiovascular risk. In these patients, it is reasonable to use alternative lipid-lowering agents in addition to statins. Among these lipid-lowering agents, ezetimibe and PCSK9 inhibitors are the most commonly used, while fibrates, nicotinic acid preparations and ω3-polyunsaturated fatty acids (ω3-PUFAs) are less common [19].

In a large-scale IMPROVE-IT RCT (including a total of 18,144 patients with acute coronary syndrome (ACS),4533 of them having T2DM), ezetimibe, an intestinal cholesterol absorption inhibitor, in combination with statins demonstrated an additional decrease in LDL-C and improvement of cardiovascular prognosis; these effects appeared to be more pronounced in patents with T2DM than without [13].

In recent RCTs: FOURIER (27,564 patients with atherosclerotic cardiovascular disorders, 11,031 of them with diabetes mellitus) and ODYSSEY OUTCOMES (18,924 patients with a recent experience of ACS, 5444 of them with T2DM), PCSK9 inhibitors such as evolocumab and alirocumab in combination with statins showed an effective reduction in LDL-C and a pronounced positive effect on cardiovascular prognosis. These favorable changes did not depend on the presence of diabetes mellitus [22, 23].

The international experts have used the data from the three RCTs mentioned above as the grounds to support "the lower, the better" concept in respect of the relationship between the LDL-C levels and the cardiovascular risk (some experts suggest modifying the concept name with the same aphoristic connotation: "lower, faster, younger", without an explicit lower threshold of proven benefit). Currently, some experts consider LDL-C concentrations that are unusually low for routine cardiological practice,

such as <1.0 mmol/L (and even <0.65 mmol/L) to be desirable for individuals with extremely high cardiovascular risk (including those with T2DM, peripheral artery lesions, recent MI, history of recurrent cardiovascular events). It is emphasized that the existing evidence of long-term safety of such low concentrations of LDL-C are still limited and require additional confirmation. In general, it is considered that ezetimibe and/or PCSK9 inhibitors are indicated to the patients with T2DM and CHD in addition to statins, provided the LDL-C levels on the treatment with maximum tolerated doses of the latter are maintained at the level of ≥1.4 mmol/L [17].

Several RCTs studied the opportunities to lower the cardiovascular risk under the influence of other lipid-lowering agents, used in addition to statins. In these studies, fibrates, nicotinic acid preparations, and various representatives of ω3-PUFAs failed to demonstrate distinct favorable cardiovascular effects, which led to a significant weakening of the position of these drug products in primary and secondary prophylaxis strategies. The use of fibrates and ω3-PUFAs in patients with T2DM and CHD is reserved for the cases with pronounced hypertriglyceridemia (1.5–5.6 mmol/L according to the European guidelines) to reduce the risk of pancreatitis [18, 24].

The data from REDUCE-IT RCT (8179 patients with atherosclerotic cardiovascular disorders, including 4730 patients with T2DM, who had TG levels of 1.5–5.6 mmol/L) can be a significant recent addition to the possibilities of lipid-lowering therapy. In this RCT, icosapent ethyl in the dose of 2 g twice daily showed a clear reduction of cardiovascular risk. This drug product (it is emphasized that the obtained results should not be extrapolated to other variants of ω3-PUFAs) are currently considered as the first-line therapy in patients with T2DM and CHD, provided the TG levels in these patients remain at a level of >1.5 mmol/L, according to ESC guidelines, in spite of the use of the maximum tolerated dose of statins and lifestyle changes [18, 25].

Lipid-lowering agents and cognitive function

Previous concerns about cognitive function deterioration on treatment with statins and other lipid-lowering agents are currently recognized as not supported by substantial evidence; therefore, these concerns should not prevent physicians from prescribing these drug products for appropriate indications [13].

Use of glucose-lowering agents

Intensive glycemic control was earlier considered to be the leading principle for reducing the risk of complications in patients with T2DM, including coronary events. The treatment strategy (referred to as ***glucocentric***) was primarily focused on the achievement and maintenance of target HbA_{1C} levels; no preferences to any glucose-lowering agents were given [1]. However, a number of RCTs later showed no improvement in cardiovascular prognosis in patients with T2DM with intensive glycemic control (with HbA_{1C} reduction to <6 %–6.5 %) compared to standard control. Moreover, several studies showed that glucose-lowering agents of various classes have a different effect on cardiovascular prognosis despite similar glycemia reduction. This led to the transformation of glycemic control strategy in T2DM into a ***differential*** one, giving preference to glucose-lowering agents with proven organic protective properties [26].

Target glycemic levels in patients with T2DM and chronic CHD

Although more intensive glycemic reduction with achievement of relatively low (6.5 %–7.0 %) HbA_{1C} levels is associated with a reduced risk of microvascular complications of T2DM (retinopathy, nephropathy, peripheral neuropathy), and, possibly, the risk of stroke, it is not related to a reduction in overall mortality, cardiovascular mortality and the incidence of cerebral stroke while maintaining the specified HbA_{1C} values. The largest RCTs (UKPDS, ADVANCE, ACCORD, VADT) did not show significant differences in the incidence of cardiovascular events in groups with more intensive glycemic control (mean HbA_{1C} 6.4 %–7.0 %) compared to groups where the control was less intensive (HbA_{1C} levels 7.3 %–8.4 %). Epidemiological studies and registries also suggest that the association between HbA_{1C} levels and mortality in patients with T2DM and cardiovascular disorders is U-shaped, where the lowest mortality rates correspond to HbA_{1C} values between 7.0 % and 8.0 %. These data were reflected in current guidelines of leading world endocrinology and cardiology associations, stating that

(1) HbA_{1C} levels 6.5 %–7.0 % can be used as target levels mainly in patients with T2DM who have sufficiently long-life expectancy and do not have significant comorbidities, DM complications, or episodes of severe hypoglycemia;

(2) HbA_{1C} levels of 7.0 %–8.0 % are more suitable for older patients with T2DM who have a moderate life expectancy, microvascular and macrovascular complications of DM, episodes of severe hypoglycemia, significant comorbidities; these particular values of HbA_{1C} are recommended by experts as target for the majority of patients with T2DM and chronic CHD;

(3) HbA_{1C} levels of 8.0 %–8.5 % may be considered as target for a limited category of most severe patients with T2DM who have limited life expectancy, pronounced microvascular and macrovascular complications of DM, severe comorbidities (end-stage renal, respiratory or heart failure, pronounced dementia, incurable cancer lesions) [27].

Risk of hypoglycemia

Several RCTs showed a 2–3-fold increase in the risk of pronounced hypoglycemia in patients with T2DM whose treatment provided for more intensive control of HbA_{1C}. Adverse effects of these episodes are not limited to the known combination of clinical signs; its sequelae include falls, injuries, road accidents, coma, and death. Moreover, the patients with concomitant cardiovascular disorders, episodes of hypoglycemia are associated with an increased cardiovascular risk, although the nature of this relationship requires further studies. For this reason, it is recommended that episodes of hypoglycemia in patients with diabetes mellitus, especially those with cardiovascular disorders (including CHD) should be minimized [28].

Sulfonylureas and insulins

Taking into account the high coronary risk typical of diabetes mellitus, as well as the wide differences in the mechanisms of action of the available glucose-lowering agents, the issue of the possible presence of special cardioprotective properties of certain classes of drug products is very important.

Cardiovascular safety of sulfonylurea derivatives has previously raised concerns among clinicians. The mechanism of glucose-lowering effect of these drug products involves membrane depolarization of pancreatic β cells with increased insulin release. Sulfonylurea-associated hyperinsulinemia, increased risk of hypoglycemia and impaired ischemic preconditioning were considered as factors that could potentially increase the cardiovascular risk. However, although the use of these drug products was associated with some increase in the risk in several retrospective epidemiological analyses, in the majority of large-scale controlled trials, their use (especially second-generation drugs such as glimepiride in the CAROLINA RCT) with respect to cardiovascular prognosis was quite neutral. in the UKPDS RCT, sulfonylurea derivatives demonstrated a reduction in the risk of microvascular complications of T2DM (especially of retinopathy and DNP [29].

For the same reasons as sulfonylureas, insulin preparations have previously been considered as ambiguous with regard to cardiovascular safety. The epidemiological studies of insulin preparations noted an increase in the cardiovascular risk; at the same time, the need for careful interpretation of these results is emphasized, since these drug products are usually reserved for a more severe category of patients. In the RCTs, the use of insulin preparations was accompanied by a reduced risk of microvascular complications of DM; their effect on the cardiovascular prognosis was neutral.

The available data allow the experts to consider careful use of sulfonylureas and insulin in patients with T2DM and chronic CHD, but not as first-line glucose-lowering therapies. This is all the more important because glycemic control products with proven favorable cardiovascular effects are already available to the physician [30].

Metformin, unlike sulfonylureas and insulin preparations, may have a positive effect on cardiovascular prognosis (UKPDS RCT), its use does not increase the risk of hypoglycemia and body weight. There is an ongoing large-scale RCT with prolonged used extended-release metformin (VA-IMPACT, 7868 patients with pre-diabetes and atherosclerotic cardiovascular disorders); the results are expected in 2024. Current guidelines on the treatment of patients with diabetes mellitus still consider metformin as the first-line glucose-lowering therapy and the most popular in patients with T2DM and chronic CHD in the developed countries [30].

Thiazolidinediones, due to their ability to increase insulin sensitivity ("insulin sensitizers "), were initially considered as promising therapies for persons with T2DM and CHD. Further, some ambiguous data concerning the effect of this class a representative (rosiglitazone) on cardiovascular prognosis provided the basis for alarming preliminary conclusions and limitations to their use. Although the results of representative RCTs (PROACTIVE, 5238 patients; IRIS, 3876 patients, with pioglitazone, and RECORD, 4447 patients, with rosiglitazone) in patients with T2DM and atherosclerotic cardiovascular disorders demonstrated favorable or neutral effects; practicing physicians still express some doubt regarding their use. These drug products may induce sodium and water retention, and thus deteriorating clinical signs of heart failure (HF). They are contraindicated for patients with chronic HF, and should be used with care in patients with CHD without HF [31].

Dipeptidyl peptidase-4 inhibitors (DPP-4i)

The controversial nature of the data on the effect of thiazolidinediones on cardiovascular risk is one of the reasons why the world's leading regulatory agencies, the US Food and Drug Administration, and the European Medicines Agency have made a decision not to authorize new blood glucose-lowering agents without conclusive evidence of cardiovascular safety in large RCTs. The first class of drug products subject to these studies were DPP-4i. These drug products increase the levels of endogenous incretins, elevate the production of insulin, and reduce glucagon release. The degree of the glucose-lowering effect of DPP-4i is lower than for the drug products listed above, but they do not increase the risk of hypoglycemia, do not increase body weight, and are well-tolerated. Representative RCTs of DPP-4i in the patients with T2DM demonstrated neutral effects on cardiovascular and renal

prognosis: (1) SAVOR TIMI-53 (16,492 patients, saxagliptin); (2) EXAMINE (5380 patients, alogliptin); (3) TECOS (14,671 patients, sitagliptin); (4) CARMELINA (6979 patients, linagliptin) [32].

Sodium-glucose linked transporter-2 inhibitors (SGLT-2is) were the first class of glucose-lowering agents that demonstrated an apparent beneficial effect on the cardiovascular and renal prognosis in patients with T2DM. These drug products increase glucose excretion in urine (≥100 g/day, which results in glycemia decrease), induce natriuretic, diuretic action and a complex of additional (pleiotropic) effects. Their use is associated with a moderate reduction in HbA_{1C} (by 0.3 %–0.6 %), systolic and diastolic BP (by 3–4 and 1–2 mm Hg), weight loss (by 2–3 kg). An increased risk of genital mycotic infections in both genders is reported among side effects, which is associated with glycosuria induced by their administration. Standard hygiene measures (daily shower) can help reduce the risk of these infections, and successful management of most manifested cases can be achieved through the use of topical antifungal agents. A positive effect of some representatives of SGLT-2is on the cardiovascular prognosis with a significant reduction in the rate of hospitalizations for heart failure, a decrease in cardiovascular and overall mortality was demonstrated for patients with T2DM and atherosclerotic cardiovascular disorders in RCTs: (1) EMPA-REG OUTCOME (7020 patients, empagliflozin); (2) EMPEROR-REDUCED (3730 patients, empagliflozin); (3) CANVAS (10,142 patients, canagliflozin); (4) DECLARE TIMI-58 (17,160 patients, dapagliflozin). Renoprotective effects (decrease in albuminuria, decrease in the rate of progression to end-stage renal failure and decrease in death from renal causes) have also been shown for all these drug products [33–36].

Glucagon-like peptide-1 receptor agonists (GLP-1-RAs) are mainly used as subcutaneous injections (only one of GLP-1-RAs — semaglutide — has an oral dosage form). These drug products, similar to DPP-4i, influence the incretin system and stimulate glucose-dependent insulin release by pancreatic islet cells; they also slow gastric emptying and reduce appetite. Side effects of GLP-1-RAs include dose-dependent gastrointestinal events (nausea, vomiting, diarrhea); injection site reactions (hypersensitivity reactions) are also possible. The use of GLP-1-RAs is associated with a more significant decrease in HbA_{1C} levels and weight loss compared to DPP-4i and SGLT-2i. In several large-scale RCTs, drug products of this class demonstrated beneficial effects on cardiovascular prognosis in the patients with T2DM with atherosclerotic cardiovascular disorders or a high risk thereof: (1) LEADER (9340 patients, liraglutide); (2) SUSTAIN-6 (3297 patients, semaglutide); (3) REWIND (9901 patients, dulaglutide); in AWARD-7 RCT, dulaglutide also demonstrated its renoprotective effects [37–39].

Taking into account the data from numerous RCTs, the experts state that the choice of a hypoglycemic agent is of great importance. Some glucose-lowering agents provide proven cardio-, vaso-, and renoprotection and are already considered to be preferable in the updated guidelines of the national and world medical associations (endocrinologists, cardiologists, nephrologists). In particular, GLP-1-RAs and SGLT-2i for which cardioprotective effects have been demonstrated are considered the glucose-lowering agents of choice (usually in combination with metformin) for patients with T2DM who have a high cardiovascular risk (including CHD). If a patient has apparent clinical signs of HF, the preference should be given to SGLT-2i. The same class also has benefits for patients with DNP at the levels of glomerular filtration rate (GFR) ≥30 mL/min/1.73 m^2 (at the same time, the GLP-1-RA representative, dulaglutide can be used at GFR > 15 mL/min/1.73 m^2) [38, 40, 41].

Diagnostic approaches in a patient with stable angina

The use of most non-invasive and invasive investigation methods in patients with chronic CHD (including electrocardiography, echocardiography, exercise ECG/Echo ECG testing, radionuclide methods, coronary arteriography) do not depend significantly on the presence or absence of diabetes mellitus. Several recent trials (SCOT-HEART, PROMISE) demonstrated that in patients with T2DM and chronic CHD, coronary computed tomographic angiography compared to cardiac exercise stress tests can better diagnose nonobstructive coronary lesions and, due to this, improve the quality of medical treatment [42].

Antianginal therapy

In spite of the use of modern cardio- and vasoprotective medical therapies, as well as revascularization methods, clinical signs of angina are found in about 1/3 patients with stable CHD. Patients with T2DM and clinical signs of angina often have more common and severe coronary events compared to patients with patients without DM, which can be a restriction for revascularization [43].

Choice of antianginal agents

Drug products (1) that increase myocardial oxygen supply (nitrates, CCBs) and (2) that decrease myocardial oxygen consumption (β-ABs, CCBs, ivabradine, trimetazidine, ranolazine) can be used to relieve angina. Current

national and foreign guidelines provide for the use of β-ABs and/or CCBs, reserving other classes of antianginal agents for the cases of resistance or lack of effect of the first-priority drugs. In patients with stable CHD (in the absence of recent MI and heart failure), there is no convincing evidence that any of the above classes of antianginal agents can reduce the risk of MI and mortality; moreover, their effects on angina severity and exercise tolerance are considered to be very similar. In this regard, the choice of antianginal agents in people with T2DM should be primarily guided by their effects on BP and pulse rate, the nature of side effects, cost, and influence on glycemic levels. Approaches to the choice of a specific class of these drug products in patients with stable angina and diabetes mellitus are largely standard. As in patients without T2DM, it should be borne in mind that the use of nondihydropyridine CCBs in patients with LV systolic dysfunction and in those receiving β-ABs is undesirable. For long-acting nitrates, it is important to consider the risk of resistance and endothelial dysfunction in the absence of an adequate nitrate-free interval during long-term use [42].

Many representatives of β-ABs are effective antianginal agents and have metabolic side effects. β-ABs reduce the heart rate and myocardial contractility, therefore, reducing its oxygen demand. Compensatorily, this induces vasoconstriction, which, in turn, increases insulin resistance and leads to the formation of atherogenic lipid profile. β-ABs that have additional vasodilator effects (carvedilol, nebivolol) have either a favorable or neutral effect on metabolic parameters. In comparative studies in patients with T2DM, vasodilating β-ABs compared to non-vasodilating representatives of this class demonstrated a small but significant decrease in HbA_{1C} (by 0.1 %–0.2 %), improved insulin resistance, decreased cholesterol levels, weight loss, and slower rate of microalbuminuria development [31].

Among antianginal agents used in patients with T2DM, ranolazine, a selective inhibitor of the cardiomyocyte sodium channels, has been well studied. In addition to an effective reduction in angina activity, it influences glucagon secretion, which is accompanied by a decrease in HbA_{1C} levels by about 0.5 %–0.7 %. Both antianginal and glucose-lowering effects of ranolazine are more pronounced in patients with poorly controlled diabetes mellitus [44].

In patients with T2DM, combination antianginal therapy can include ivabradine and trimetazidine. Their antianginal activity does not depend on the presence of diabetes mellitus. Both drug products are metabolically neutral and have no influence on BP. Ivabradine is only used in patients with sinus rhythm; it can cause clinically significant bradycardia; in the presence of left ventricular systolic dysfunction, it has a beneficial effect on cardiovascular prognosis. Trimetazidine has no effect on the heart rate; it is contraindicated for patients with Parkinson disease and restless leg syndrome [42].

Revascularization opportunities

In patients with T2DM and CHD, treatment is based on optimal medical therapy (OMT includes the above-mentioned approaches to prognosis improvement and antianginal agents, if necessary) in combination with lifestyle changes. However, the importance of revascularization approaches increases together with increasing severity and prevalence of coronary events. The outcomes of surgical and transcutaneous revascularization in patients with T2DM are worse compared to patients without DM, including a higher risk of peri-procedural complications and coronary restenosis. The benefit/risk balance for each of revascularization approaches varies and depends on peculiarities of coronal anatomy, comorbidities and some other factors, thus requiring an individual approach to treatment strategy. In patients with multivessel stenosis, left main coronary artery involvement, complex coronal anatomy, coronary artery bypass grafting (CABG) compared to percutaneous coronary intervention (PCI) is associated with a decreased incidence of long-term major cardiovascular events (RCTs: BARI 2D, COURAGE, FREEDOM) with a slightly increased risk of stroke in the early period (the incidence of stroke within the first 30 days is 1.8 % after CABG, 0.3 % after PCI). The lower incidence of cardiovascular events post CABG may be related to greater completeness of coronary revascularization achieved in this intervention [43–46].

Summing up the data from RCTs conducted in recent years, the experts of American Heart Association and European Society of Cardiology note that the main indications for coronary revascularization in patients with T2DM in addition to OMT include (1) insufficient control of clinical manifestations of ischemia despite OMT; (2) the presence of widespread myocardial ischemia; (3) significant stenosis of left main coronary artery or proximal lesion of left anterior descending coronary artery. If coronary revascularization is indicated to a patient with T2DM, optimal approaches in addition to OMT are PCI via radial access and new generation coated stents, or CABG with shunt implantation preferably from the left a. thoracica interna (internal mammary artery). When selecting a revascularization method, individual approach, taking into account the state of coronal anatomy (SYNTAX index, etc.), cardiovascular risk profile, character of clinical manifestations and patient's preferences, is required for persons with multivessel coronary artery disease, left main coronary artery involvement, proximal stenosis of left anterior descending coronary

artery, multiple comorbidities, and decreased LV EF. Herewith, it is important to understand that the combination of OMT and CABG is the most beneficial for prognosis improvement in the majority of patients with diabetes mellitus and the above-mentioned peculiarities [47–50].

To conclude the discussion, let us emphasize the multidisciplinary nature of the issue of concomitant CHD and T2DM A decision on treatment strategy requires involvement of several medical specialists: cardiologist, endocrinologist, cardiovascular surgeon, probably, nephrologist, etc., with mandatory consideration of currently accepted national and international guidelines. The use of an integrative approach, including education of patients and their relatives, adequate changes in lifestyle, BP control, prescription of modern antithrombotic and lipid-lowering agents, differential choice of glucose-lowering agents with cardioprotective potential, weighted use of antianginal and revascularization methods will improve the quality of life and cardiovascular prognosis in the patient group under discussion.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

Щукина Е.В. (ORCID ID: https://orcid.org/0000-0002-9022-6155): разработка концепции и дизайна, обзор англоязычных публикаций по теме статьи, написание первой версии статьи, ответственная за все аспекты работы

Приколота О.А. (ORCID ID: https://orcid.org/0000-0002-2127-6925): проверка критически важного интеллектуального содержания, одобрение окончательной версии статьи перед подачей для публикации.

Багрий В.А. (ORCID ID: https://orcid.org/0000-0001-9720-0276): анализ и интерпретация данных, обзор русскоязычных публикаций по теме статьи, одобрение окончательной версии статьи перед подачей для публикации.

Андрусяк А.Ю. (ORCID ID: https://orcid.org/0000-0001-5436-7463): анализ и интерпретация данных, написание первой версии статьи, одобрение окончательной версии статьи перед подачей для публикации.

Рыбалко Г.С. (ORCID ID: https://orcid.org/0000-0002-7536-981X): научная консультация, одобрение окончательной версии статьи перед подачей для публикации.

Шестерина Ю.Б. (ORCID ID: https://orcid.org/0000-0001-8877-0066): анализ и интерпретация данных, редактирование текста, одобрение окончательной версии статьи перед подачей для публикации.

Стефано Е.А. (ORCID ID: https://orcid.org/0000-0002-3513-3212): анализ и интерпретация данных, редактирование текста, одобрение окончательной версии статьи перед подачей для публикации.

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Shchukina E.V. (ORCID ID: https://orcid.org/0000-0002-9022-6155): development of the concept and design, review of English-language publications on the topic of the article, wrote the first version of the article, responsible for all aspects of the work

Prikolota O.A. (ORCID ID: https://orcid.org/0000-0002-2127-6925): verification of critical intellectual content, final approval for publication of the manuscript

Bagrij V.A. (ORCID ID: https://orcid.org/0000-0001-9720-0276): contributed to the analysis and interpretation of the data, review of Russian-language publications on the topic of the article, approved the final version of the article before submitting it for publication

Andrusjak A.Ju. (ORCID ID: https://orcid.org/0000-0001-5436-7463): contributed to the analysis and interpretation of the data, wrote the first version of the article, approved the final version of the article before submitting it for publication

Rybalko G.S. (ORCID ID: https://orcid.org/0000-0002-7536-981X): scientific advising, final approval for publication of the manuscript

Shesterina Yu.B. (ORCID ID: https://orcid.org/0000-0001-8877-0066): contributed to the analysis and interpretation of the data, text editing, final approval for publication of the manuscript

Stefano E.A. (ORCID ID: https://orcid.org/0000-0002-3513-3212): contributed to the analysis and interpretation of the data, text editing, final approval for publication of the manuscript

Список литературы/References:

1. Ferrannini G, De Bacquer D, De Backer G, et al. EUROASPIRE V collaborators. Screening for glucose perturbations and risk factor management in dysglycemic patients with coronary artery disease — a persistent challenge in need of substantial improvement: a report from ESC EORP EUROASPIRE V. Diabetes Care. 2020;43(4): 726–733. doi:10.2337/dc19-2165.
2. Ferranini G., Norhammar A., Gyberg V. et al. Is coronary artery disease inevitable in type 2 diabetes? From a glucocentric to a holistic view on patient management. Diabetes Care. 2020; 43 (9): 2001-2009. doi: 10.2337/dci20-0002.
3. Arnett DK, Blumenthal RS, Albert MA et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology. American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019; 140: 596–646. doi: 10.1161/ CIR.0000000000000678
4. Evert AB, Dennison M, Gardner CD et al. Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report. Diabetes Care. 2019; 42(5): 731-754. doi:10.2337/dci19-0014
5. Boer de L., Caramori M., Chan J. et al. Executive summary of the 2020 KDIGO Diabetes management in CKD Guideline: Evidence-based advances in monitoring and treatment. Kidney Int.2020; 98: 839–848. doi:10.1016/j.kint.2020.06.024
6. Arnold SV, Bhatt DL, Barsness GW, et al. Clinical management of stable coronary artery disease in patients with type 2 diabetes mellitus: a scientific statement from the American Heart Association. Circulation. 2020; 141: 779–806. doi: 10.1161/CIR.0000000000000766
7. Colberg SR, Sigal RJ, Yardley JE, et al. Physical activity/exercise and diabetes: a position statement of the American Diabetes Association. Diabetes Care. 2016; 39: 2065–2079. doi: 10.2337/dc16-1728
8. Newman J.D., Schwartzbard A.Z., Weintraub H.S., et al. Primary prevention of cardiovascular disease in diabetes mellitus. JACC. 2017; 70(7): 883-893. doi: 10.1016/j.jacc.2017.07.001
9. Cosentino F. GPJ, Aboyans V., Bailey C.J. et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). European Heart Journal. 2020; 41(2): 255-323. doi:10.1093/eurheartj/ehz486.

10. Bates E.R. Antiplatelet therapy in patients with coronary disease and type 2 diabetes. N Engl J Med. 2019; 381(14): 1373-1375. doi: 10.1056/NEJMe1910813
11. Joshua J. Joseph, Prakash Deedwania, Tushar Acharya, et al. Comprehensive Management of Cardiovascular Risk Factors for Adults With Type 2 Diabetes: A Scientific Statement From the American Heart Association. Circulation. 2022; 145: 722–759. doi:10.1161/CIR.0000000000001040.
12. Connolly SJ, Eikelboom JW, Bosch J, et al; COMPASS Investigators. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet. 2018; 391: 205–218. doi: 10.1016/S0140-6736(17)32458-3
13. American Diabetes Association. 10. Cardiovascular disease and risk management: Standards of Medical Care in Diabetes. 2020. Diabetes Care. 2020; 43(1): 111–134. doi.org/10.2337/dc20-s010
14. Deedwania P. The ongoing saga of optimal blood pressure level in patients with diabetes mellitus and coronary artery disease. J Am Heart Assoc. 2018; 7: e010752. doi: 10.1161/JAHA.118.010752
15. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016; 387: 957–967. doi: 10.1016/S0140-6736(15)01225-8
16. Goldberg R.B., Stone N.J., Grundy S.M. The 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guidelines on the Management of Blood Cholesterol in Diabetes. Diabetes Care 2020; 43(8): 1673-1678. doi.org/10.2337/dci19-0036
17. Berberich A., Hegele R.A. LDL cholesterol: lower, faster, younger? Lancet Diabetes Endocrinology. 2020; 8(1): 5-7. doi:10.1016/S2213-8587(19)30389-4.
18. François M, Colin B, Alberico LC, et. al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). European Heart Journal. 2020; 41 (1): 111–188. doi.org/10.1093/eurheartj/ehz455
19. Grundy SM, Stone NJ, Bailey AL, et al., 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. Journal of the American College of Cardiology. Circulation. 2019; 73 (24): 285–350. doi:10.1016/j.jacc.2018.11.003.
20. Erqou S, Lee CC, Adler AI. Statins and glycaemic control in individuals with diabetes: a systematic review and meta-analysis. Diabetologia. 2014; 57: 2444–2452. doi: 10.1007/s00125-014-3374-x
21. Newman C.B., Preiss D., Tobert J.A. et al. Statin safety and associated adverse events: A scientific statement from the American Heart Association.Arteriosclerosis, Thrombosis and Vascular Biology. 2019; 39(2): 38-81. doi: 10.1161/ATV.0000000000000073.
22. Смолина М.О., Бенимецкая К.С., Рагино Ю.И. и др. PCSK9: новые победы и горизонты. Атеросклероз. 2018; 14(3): 70-77. doi: 10.15372/ATER20180311.
Smolina M.O., Benimeckaja K.S., Ragino Ju.I. PCSK9: new victories and horizons. Atherosclerosis. 2018; 14(3): 70-77. doi: 10.15372/ATER20180311. [In Russian]
23. Landmesser U, Chapman MJ, Stock JK et al. 2017 Update of ESC/ EAS Task Force on Practical Clinical Guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia. Eur Heart J. 2018; 39: 1131–1143. doi: 10.1093/eurheartj/ehx549
24. Bowman L., Mafham M., Wallendszus K. et al. Effects of n-3 fatty acid supplements in diabetes mellitus . N Engl J Med. 2018; 379: 1540-50. doi: 10.1056/NEJMoa1804989
25. Bhatt DL, Steg PG, Miller M et al; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapentethyl for hypertriglyceridemia. N Engl J Med. 2019; 380: 11–22. doi: 10.1056/NEJMoa1812792
26. Abhinav Sharma, Neha J. Pagidipati, et al. Impact of Regulatory Guidance on Evaluating Cardiovascular Risk of New Glucose-Lowering Therapies to Treat Type 2 Diabetes Mellitus Lessons Learned and Future Directions. Circulation. 2020; 141: 843–862. doi: 10.1161/CIRCULATIONAHA.119.041022
27. American Diabetes Association. 6. Glycemic targets: Standards of Medical Care in Diabetes 2020. Diabetes Care. 2020; 43(1): 66–76. doi:10.2337/dc20-S006.
28. Lee AK, Warren B, Lee CJ, et al. The association of severe hypoglycemia with incident cardiovascular events and mortality in adults with type 2 diabetes. Diabetes Care. 2018; 41: 104–111. doi: 10.2337/dc17-1669
29. Ворожцова И.Н., Будникова О.В., Афанасьев С.А. и др. Влияние сахарного диабета 2-го типа на миокард пациентов с ишемической болезнью сердца. Сибирский медицинский журнал. 2018; 33(1): 14-20. doi: 10.29001/2073-8552-2018-33-1-14-20
Vorozhcova I.N., Budnikova O.V., Afanas'ev S.A. The effect of type 2 diabetes mellitus on the myocardium of patients with coronary heart disease. Siberian medical journal.2018; 33(1): 14-20. doi: 10.29001/2073-8552-2018-33-1-14-20. [In Russian]
30. Багрий А.Э., Супрун Е.В., Михайличенко Е.С. и др. Хроническая сердечная недостаточность и сахарный диабет 2 типа: состояние проблемы. Российский кардиологический журнал. 2020; 25(4): 3858. doi:10.15829/1560-4071-2020-3858.
Bagrij A.Je., Suprun E.V., Mihajlichenko E.S. Chronic heart failure and type 2 diabetes mellitus: state of the problem. Russian Journal of Cardiology. 2020; 25(4): 3858. doi:10.15829/1560-4071-2020-3858 [In Russian]
31. Дедов И.И., Шестакова М.В., Майоров А.Ю. и др. Сахарный диабет 2 типа у взрослых. Клинические Рекомендации. Сахарный диабет. 2020; 23(2): 4-102. doi: 10.14341/DM12507.
Dedov I.I., Shestakova M.V., Majorov A.Ju. Type 2 diabetes mellitus in adults. Clinical Guidelines. Diabetes mellitus. 2020; 23(S2): 4-102. doi: 10.14341/DM12507. [In Russian].
32. Liu D, Jin B, Chen W, et al. Dipeptidyl peptidase 4 (DPP-4) inhibitors and cardiovascular outcomes in patients with type 2 diabetes mellitus (T2DM): a systematic review and meta-analysis. BMC Pharmacol Toxicol. 2019; 20: 15. doi:10.1186/s40360-019-0293-y
33. Шумилова Н.А., Павлова С.И. Глифлозины: гликемические и негликемические эффекты. Acta medica Eurasia. 2019; 1: 44-51. doi:acta-medica-eurasica.ru/single/2019/1/6/.
Shumilova N.A., Pavlova S.I. Glyflozins: Glycemic and Non-glycemic Effects. Acta medica Eurasia. 2019; 1: 44-51. doi:acta-medica-eurasica.ru/single/2019/1/6/ [In Russian]
34. Heerspink H.J.L., Stefansson B.V., Chertow G.M. et al. Rationale and protocol of the Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) randomized controlled trial. Nephrol Dial Transplant. 2020; 35: 274–282. doi:10.1093/ndt/gfz290.
35. Lo K.B., Gul F., Ram P. et al. The Effects of SGLT2 Inhibitors on Cardiovascular and Renal Outcomes in Diabetic Patients: A Systematic Review and Meta-Analysis. Cardiorenal Med. 2020; 10: 1–10. doi:10.1159/000503919.

36. Perkovic V., Jardine M.J., Neal B. et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019; 380: 2295-2306. doi: 10.1056/NEJMoa1811744.
37. Kristensen SL, Rorth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol .2019; 7: 776-785. doi:10.1016/S2213-8587(19)30249-9.
38. Ghosh-Swaby O.R., Goodman S.G., Leiter L.A. et al. Glucose-lowering drugs or strategies, atherosclerotic cardiovascular events, and heart failure in people with or at risk of type 2 diabetes: an updated systematic review and meta-analysis of randomized cardiovascular outcome trials. Lancet Diabetes and Endocrinology. 2020; 8(5): 418-435. doi:10.1016/S2213-8587(20)30038-3
39. Marso SP, Daniels GH, Brown-Frandsen K et al; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016; 375: 311–322. doi: 10.1056/NEJMoa1603827
40. Bonora B.M., Avogaro A., Fadini G.P. Extraglycemic effects of SGLT2 Inhibitors: A review of the evidence. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2020; 13: 161–174. doi: 10.2147/DMSO.S233538
41. Buse JB, Wexler DJ, Tsapas A, et al. 2019 Update to: management of hyperglycemia in type 2 diabetes, 2018: a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2020; 43: 487–493. doi: 10.2337/dci19-0066
42. Knuuti J., Wijns W., Saraste A. et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur. Heart J. 2020; 41: 407-477. doi:10.1093/eurheartj/ehz425.
43. Mancini GBJ, Boden WE, Brooks MM et al. Impact of treatment strategies on outcomes in patients with stable coronary artery disease and type 2 diabetes mellitus according to presenting angina severity: a pooled analysis of three federally-funded randomized trials. Atherosclerosis. 2018; 277: 186–194. doi: 10.1016/j.atherosclerosis.2018.04.005
44. Kosiborod M, Arnold SV, Spertus JA et al. Evaluation of ranolazine in patients with type 2 diabetes mellitus and chronic stable angina: results from the TERISA randomized clinical trial (Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina). J Am Coll Cardiol. 2013; 61: 2038–2045. doi: 10.1016/j.jacc.2013.02.011
45. Mancini GBJ, Boden WE, Brooks MM et al. Impact of treatment strategies on outcomes in patients with stable coronary artery disease and type 2 diabetes mellitus according to presenting angina severity: a pooled analysis of three federally-funded randomized trials. Atherosclerosis. 2018; 277: 186–194. doi: 10.1016/j.atherosclerosis.2018.04.005
46. Farkouh ME, Domanski M, Dangas GD et al; FREEDOM Follow-On Study Investigators. Long-term survival following multivessel revascularization in patients with diabetes: the FREEDOM Follow-On Study. J Am Coll Cardiol. 2019; 73: 629–638. doi: 10.1016/j.jacc.2018.11.001
47. Bhatt DL. CABG the clear choice for patients with diabetes and multivessel disease. Lancet. 2018; 391: 913–914. doi: 10.1016/S0140-6736(18)30424-0
48. Neumann FJ, Sousa-Uva M, Ahlsson A et al; ESC Scientific Document Group. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J. 2019; 40: 87–165. doi:10.1093/eurheartj/ehy394
49. Doenst T, Haverich A, Serruys P, et al. PCI and CABG for treating stable coronary artery disease: JACC review topic of the week. J Am Coll Cardiol. 2019; 73: 964–976. doi: 10.1016/j.jacc.2018.11.053
50. Head SJ, Milojevic M, Daemen J. et al. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. Lancet. 2018; 391: 939–948. doi: 10.1016/S0140-6736(18)30423-9