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EXPERT OPINION

Updated European guidelines on pre-diabetes, diabetes and cardiovascular disease: Opinion of Russian experts

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The updated ESC Guidelines on pre-diabetes, diabetes and cardiovascular disease developed by the experts of two European societies were introduced at the 2019 ESC Congress of Cardiology (August 31 — September 4 in Paris, France). The updated guidelines present information on prioritizing different types of hypoglycemic therapy based on its cardiovascular effects, target lipid levels in patients with diabetes depending on cardiovascular risk, and information on antiplatelet therapy administration.

We present Russian experts' comments on the broad spectrum of questions that were introduced in the updated guidelines.

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The updated ESC Guidelines on pre-diabetes, diabetes and cardiovascular disease were introduced at the 2019 ESC Congress of Cardiology (August 31 — September 4 in Paris, France). This document was developed by the European Society of Cardiology (ESC chairperson of the task force — Francesco Cosentino, Sweden) in collaboration with the European Association for the Study of Diabetes (EASD chairperson of the task force — Peter Grant, England). The updated guidelines present information on prioritizing different types of hypoglycemic therapy based on its cardiovascular effects, target lipid levels in diabetic patients depending on cardiovascular risk, information on antiplatelet therapy administration [1].

Below we present Russian experts' comments on the spectrum of questions that were introduced in the updated guidelines.

Epidemiology and definition of diabetes

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Diabetes is a serious medical and social problem worldwide. Its prevalence is steadily increasing to 10% in developing countries, primarily in India and China. As of 2017 over 60 million adult Europeans have diabetes and the majority of them have not been diagnosed yet. In general, the number of diabetic patients is expected to rise to 600 million by 2045. At the same time there are rising concerns that the age of onset has decreased, and diabetes is now occurring at a younger age [2].

Diabetes and pre-diabetes classification is based on the World Health Organization (WHO) (2006/2011) and the ADA (2019) recommendations [2, 3]. Further investigations are needed in order to determine the effect of gender, ethnicity and age on the diagnostic criteria.

Prediabetes is characterized by impaired fasting plasma glucose (FPG) or glucose tolerance (GT) and is an intermediate stage of diabetes development [4].

Diabetes can be diagnosed with the FPG or hemoglobin A1c (HbA1c) tests. Oral glucose tolerance test (OGTT) is used to diagnose impaired glucose tolerance. Experts recommend to use HbA1c and/or FPG as screening tests in patients with documented cardiovascular disease (CVD). OGTT can be further used in these patients if the results of HbA1c or FPG are inconclusive [3, 4].

Stratification of cardiovascular risk in patients with diabetes and pre-diabetes

The 2016 European guidelines on CVD prevention presented cardiovascular risk stratification in patients with diabetes. In the updated guidelines the central principle remained unchanged [1]:

- Very high-risk group includes individuals with:
- Diabetes and CVD or other end-organ damage;> 3 risk factors;
- Long-standing type 1 diabetes (>20 years).

The high-risk group includes patients with long-standing diabetes (≥10 years) without end-organ damage and other additional risk factors, while the moderate risk group includes young patients (type 1 diabetes<35 years old, type 2 diabetes<50 years old) with diabetes lasting less than 10 years without other risk factors.

Patients with pre-diabetes can also be at high risk for CVD depending on their clinical status and the presence of other risk factors/end-organ damage. In general, risk scoring in patients with pre-diabetes is the same as in the general population, as standard charts are applied.

Prevention of cardiovascular disease in patients with pre-diabetes and diabetes.

Comprehensive measures are used to prevent CVD in patients with impaired glucose metabolism. They include lifestyle modification (diet, physical activity, smoking cessation), pharmacologic therapy to reach glycemic targets, blood-pressure target levels and target lipid levels, as well as antiplatelet therapy for primary and secondary prophylaxis [6–12].

Lifestyle modification principles remain unchanged: lower calorie intake, Mediterranean diet, and moderate physical activity of≥150 min/week. Together these changes can prevent and control DM.

Arterial hypertension

Arterial hypertension (AH) is highly prevalent in patients with DM (>60 % of cases) as well as in patients with pre-DM, which may be explained by obesity and hyperinsulinemia [13]. Multiple clinical studies show that optimal blood pressure control lowers the risk of micro- and macrovascular complications. Blood pressure targets have changed over the last years after a number of major clinical studies have been conducted. In DM patients blood pressure should be targeted to a systolic blood pressure (SBP)<130 mmHg but not<120 mmHg; and older patients with DM — to a SBP 130–139 mmHg. SBP in patients with DM should be targeted to<80 mmHg, but not<70 mmHg.

Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) are still the central components of combination therapy. Calcium channel blockers (CCBs) or diuretics can be used together with renin–angiotensin–aldosterone (RAAS) blockers. In the majority of cases two-drug regimen is indicated as the initial treatment of hypertension in DM. Of note is that pre-DM patients who take ACEIs or ARBs have lower risks of DM development compared with those who take beta-blockers or diuretics [1, 14].

Lipid-lowering therapy

New target lipid levels depending on the CVD risk have been resented in the updated guidelines:

- In patients with T2DM at moderate CVD risk the target LDL cholesterol (LDL–C) level is<2.5 mmol/l;
- In patients with T2DM at high CVD risk the target LDL–C level is<1.8 mmol/l or reduction of at least 50 %;
- In patients with T2DM at very high CVD risk the target LDL–C level is<1.4 mmol/l or reduction of at least 50 %;

Statins are still considered first-line agents. Ezetimibe can be added if maximal tolerated dose of statins is not sufficient to reach LDL–C target levels [15, 16]. In that case that a high dose of statins combined with ezetimibe is still not sufficient, addition of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors is recommended. Patients with low HDL–C levels and high triglyceride levels are administered fibrates and advised on weight loss (primarily due to reduction in fast-acting carbohydrates and alcohol consumption). Lately, risk factor correction in patients with T1DM, especially in individuals at high CVD risk, has been widely discussed. In this case statins are indicated regardless of the baseline LDL–C levels. Moreover, statins can also be considered for hypercholesterolemia in asymptomatic patients with T1DM> 30 years of age. Statins are not recommended in women of childbearing age [1].

Antiplatelet therapy

The expediency of using antiplatelets for primary prevention has been repeatedly discussed [17]. The ASCEND trial (randomized placebo-controlled study that included 15480 patients) showed that primary prevention with aspirin 100 mg daily significantly decreases the rate of cardiovascular complications (MI, stroke, transient ischemic attack, and death from any cause; p=0.02). It is suggested that in the absence of contraindications aspirin (75–100 mg daily) can be used for primary prevention in patients with DM and at very high/high risk of CVD. At the same time aspirin is not recommended for primary prevention in patients at moderate risk [18]. The use of antiplatelet therapy also rises safety issues, such as gastrointestinal bleeding. Proton pump inhibitors can be used in patients taking low-dose aspirin to protect gastric mucosa [19].

Multifactorial management

In patients with DM associated with≥2 risk factors and at high or very high risk for CVD combination therapy should be considered. Clinical studies have

shown that combination therapy for hypertension, hyperglycemia and dyslipidemia reduces the rate of cardiovascular disease by 75%. However, optimal multifactorial management strategy has not been identified. It is also not clear if there should be any differences in multifactorial management depending on gender [20, 21].

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Coronary artery disease management in patients with pre-diabetes and diabetes

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The disorders in carbohydrate metabolism worsen the prognosis of CVD [1–3]. DM is prevalent in 20–30 % of patients with coronary artery disease (CAD), and 70 % of patients have been newly diagnosed with DM or impaired glucose tolerance (IGT). Therefore, systemic evaluation of glycemic status is recommended in all patients with CAD [4, 5].

Multiple studies have shown that good glycemic control reduces the risk of microvascular complications in DM patients [6]. The emphasis is made on safety of glycemic control in CVD patients, which means that the targets for glycemic control should be individualized. Moderate glucose control has proven to be effective when compared with more intensive control. Intensive glucose control increases the risk of hypoglycemia which has a negative effect on CVD events development [7–10]. Moreover, intensive glucose control together with an unsatisfactory glycemic profile have a negative effect on CVD events frequency [11–13].

For the first time in the history of DM research the evidence of hypoglycemic agents benefits in patients at high/very high risk of CVD are presented.

Cardiovascular safety is one of the central goals of all clinical studies. Lately more attention has been drawn to new hypoglycemic agents such as glucagon-like peptide-1 (GLP-1) and sodium-glucose co-transporter-2 (SGLT2) inhibitors. Based on multiple studies of GLP-1: LEADER, SUSTAIN-6, Harmony Outcomes, REWIND и PIONEER) [14–18] and SGLT2 inhibitors (EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58 и CREDENCE) [19–22] effects these agents have been recommended for patients with DM at high/very-high cardiovascular risk regardless of whether they take metformin or not.

The benefits of GLP-1 agonists are most likely determined by reduction in atherosclerotic CVD events; SGLT2 inhibitors reduce the frequency of heart failure end-points.

Despite the lack of large randomized clinical studies of metformin effects on CVD events, it is clear that long-term use of metformin provides cardioprotective effect, decreases MI risk in DM obese patients and improves CVD prognosis [23–24].

The leading goal of CAD treatment in DM is the prevention of complications and reduction of mortality. The recommended regimen includes beta-blockers, ACEIs and CCBs.

Long-term use of oral beta-blockers leads to mortality reduction in DM patients with a history of MI, especially in those with HF (EF<40 %). Carvedilol and nebivolol are the preferred agents as they improve insulin sensitivity and don't affect glycemic profile [25, 26].

ACEIs are indicated for prevention of CVD events and HF in all patients with DM and stable CAD or acute coronary syndrome (ACS) and left ventricular (LV) systolic dysfunction [27]. ARBs can be used in patients intolerant of ACEIs. Mineralocorticoid receptor antagonists (MRA) are recommended in patients with LV systolic dysfunction or HF after MI [25, 28].

Nitrates and CCBs are indicated for relief of angina symptoms in patients taking beta-blockers who don't have contraindications for this group of agents [29].

Treatment of hypercholesterolemia is one of the most important goals in CVD prevention and CVD mortality reduction in both T1DM and T2DM. Statins are currently considered first-line agents in patients with high LDL–C levels [30]. Ezetimibe can be added if LDL–C target levels have not been achieved [15, 16]. PCSK9 inhibitors are indicated in patients at very high risk of CVD with constantly elevated LDL–C despite the use of high dose statins combined with ezetimibe or in patients intolerant of statins [33–36].

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Chronic heart failure

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Pre-DM and DM are associated with higher risk of chronic heart failure (CHF) with preserved (HFpEF) or reduced (HfrEF) ejection fraction, and 30–40 % of patients involved in clinical studies of CHF treatments had DM [1, 2]. Patients with heart failure and without DM are, at the same time, at high risk of DM development, but the underlying pathophysiological mechanisms require further investigations [3]. Patients in whom DM and CHF (especially HFrEF) coexist are at significantly higher risk of hospitalization for CHF and death from CVD or from all causes [4]. Pre-DM and undiagnosed DM in patients with CHF are associated with higher risk of death and other poor clinical outcomes [5]. Therefore, active screening for carbohydrate metabolism disorders is extremely important in this group of patients.

CHF in patients with DM is most commonly caused by CAD and AH, and prevention and treatment of these disorders result in reduced risk of CHF manifestation. The authors of the updated 2019 European guidelines of pre-DM, DM and CVD agree on the fact that hyperglycemia and insulin resistance directly affect the myocardium. At the same time, there is no conclusive evidence of the existence of specific diabetic cardiomyopathy [6].

The investigation of various CHF treatment options in patients with and without diabetes showed similar efficacy of all standard pharmacologic and non-pharmacologic regimens. The only exception was aliskiren, which is not indicated in patients with DM due to increased risk of negative side effects [7]. It is recommended to use lower dosages of ACEIs, ARBs, sacubitril/valsartan and then to gradually increase them. The follow-up of these patients should include control of potassium and creatinine. Other treatment options in patients with CHF and DM include beta-blockers, ivabradine, digoxin, diuretics, implantable cardiac defibrillator (ICD), mineralocorticoid receptor antagonists (MRA), cardiac resynchronization therapy (CRT), coronary artery bypass graft (CABG) surgery in CAD if two or three coronary vessels are involved [8].

The investigations of CVD outcomes in DM have provided the foundation for updating European guidelines of pre-DM, DM and CVD treatment in DM patients at high risk of CHF or who already have heart failure. First-line agents for DM treatment are SGLT2 inhibitors as they slow down CHF development as well as reduce mortality and the risk of hospitalizations for CHF exacerbations [9, 10]. Furthermore, according to the results of the DAPA-HF study that were pre-

sented at the 2019 ESC Congress, dapagliflozin was found to significantly reduce the total risk of cardiovascular death and hospitalizations for CHF exacerbations as well as the risk of death from any cause in patients with HFrEF with and without DM compared with placebo [11]. Although the mechanisms of such prognostic effects of SGLT2 inhibitors are not completely understood, such treatment results undoubtfully open new perspectives for CHF treatment.

Arrythmias

DM may lead to the development of atrial fibrillation (AF) due to autonomic dysfunction, electromechanical and structural remodeling, glycemic fluctuations, and atrial extrasystoles. Patients with DM and AF are at a significantly higher risk of stroke, CHF, and death from cardiovascular disease and other causes [12]. Therefore, an aggressive approach is required to prevent cardiovascular complications in such situation. As patients with AF sometimes present with only mild symptoms active detection of this type of arrythmia with an ECG is required when feasible. Oral anticoagulants are indicated to reduce the risks in AF. Kidney function should be closely monitored in DM patients in order to avoid drug accumulation and toxicity [13].

Patients with DM, both men and women, have four times increased risk of sudden cardiac death (SCD). The mechanisms behind such a high risk are probably associated with episodes of hypoglycemia that occur during an intensive hypoglycemic therapy [14] and cardiac autonomic neuropathy [15], which may cause QT prolongation. The frequency of SCD is significantly higher in patients with DM and EF<35 % [16]. For such patients and implantation of ICD is indicated. CRT is recommended in those who also have a prolongation of QRS complex [17]. Patients with DM and ventricular arrythmias should undergo the same diagnostic evaluation as those without DM (echocardiography, PCI or MRI) in order to identify cardiac structural pathology that is a more important prognostic factor compared with the presence of arrythmia. Similarly, pharmacological and non-pharmacological antiarrhythmic therapy is the same in patients with and without DM (beta-blockers, antiarrhythmic agents, catheter ablation).

Peripheral artery disease

All arteries except for the aorta, coronary and intracranial arteries are considered peripheral [18]. Peripheral artery disease (PAD) is more prevalent in patients with long-standing DM and in those with suboptimal glycemic control and with presence of known CVD risk factors [19]. Peripheral neuropathy with a reduced sensitivity to pain leads to atypical symptoms of arterial insufficiency in the lower extremities and, therefore, to late diagnosis and treatment of lower extremity artery disease (LEAD). Screening for LEAD is extremely important in patients with CAD. It is recommended to use the ankle-brachial index (ABI) to assess the presence of LEAD. The ABI< 0.9 (or> 1.4 resulting from calcinosis) usually indicated PAD and is associated with an increased risk of cardiovascular complications and death [19, 20]. Exercising for 30–45 minutes 3 times per week is indicated for patients with claudication, although the efficacy of such exercises is lower in DM [21]. Treatment of hyperglycemia can improve outcomes in limb threatening LEAD [22]. In case of severe LEAD revascularization can be considered when feasible, and only if this treatment is unavailable amputation can be performed [18]. In the COMPASS study patients with PAD (44 % with DM) were treated with a combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg once daily. At 23 months the risk of adverse limb events including amputation was reduced by 23 % (p=0.0037) compared with aspirin monotherapy [23]. The results of this study raise the possibility of a novel combination antithrombotic therapeutic regimen in high-risk vascular patients to prevent cardiovascular complications of LEAD (IIa).

Carotid artery disease should be rapidly ruled out in all patients presenting with transient ischemic attack or stroke, although systemic screening is not recommended. Carotid artery revascularization should still be considered in asymptomatic patients with one or more stroke risk factors (previous transient ischemic attack/stroke, ipsilateral silent brain infarction, stenosis progression, high-risk plaques) and if the estimated peri-operative stroke or death rate is<3 % and the patient's life expectancy is>5 years [18]. Carotid artery revascularization is indicated in symptomatic patients if the stenosis is>70 % and should be considered if the stenosis is>50 % if the estimated perioperative stroke or death rate is<6 % [18]. Carotid endarterectomy remains the standard of care and stenting can be considered as an alternative treatment in patients at high risk of post-endarterectomy complications [18]. Post-operatively, both interventions provide the same level of protection from recurrent stroke and have similar rates of repeat revascularization procedures [18]. Carotid revascularization in DM is associated with higher risk of perioperative

stroke and death [25] and restenosis with both techniques [26].

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Cardiovascular safety profile of diabetes drugs

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The latest studies showed that different types of diabetic medications affect cardiovascular diseases and their complications. This problem proved to be relevant when in 2008 the FDA decided to tighten safety requirements for hypoglycemic agents. They should not only improve the glycemia but also have safe cardiovascular profile [1]. At the same time, the principles of hypoglycemic agents use that would take into consideration the effects on cardiovascular system have not been clearly stated until now.

Concerning this issue, the 2019 ESC guidelines are a big step forward, as it divides all the hypoglycemic medications into several groups depending on their cardiovascular safety profiles.

The group of hypoglycemic drugs that clearly increase the CVD risk, primarily, the risk of CHF, include the thiazolidinediones (rosiglitazone and pio-

glitazone) [2] and the DPP-4 inhibitor saxagliptin [3], as they increase the frequency of hospitalizations of DM patients for CHF. The patients with low glomerular filtration rate (GFR≤ 60 ml/min/1.73m^2) and those with high baseline NT-proBNP have the highest risk. As such, rosiglitazone, pioglitazone and saxagliptin are contraindicated in patients with concomitant DM and CVD as well as in those patients who are at high risk of CHF.

The group of hypoglycemic agents that can increase the risk of poor cardiovascular outcomes include insulin, which retains sodium, water, and sulfonylureas, which are associated with high risk of hypoglycemia. The use of these agents in patients with CVD can be considered only after metformin and other medications that have positive effect on prognosis are administered [4].

Agents that have neutral effects on the cardiovascular system include alpha-glucosidase inhibitors (AGIs) and DPP-4 inhibitors (except for saxagliptin). A prospective study of acarbose in patients with IGT and CVD (the ACE study) showed that the use of acarbose doesn't affect the frequency of major adverse cardiac events (MACE) [5]. Cardiovascular safety of DPP-4 (gliptins) inhibitors was comprehensively assessed in several studies. Five major prospective studies have been conducted in patients with DM in order to assess cardiovascular effects of DPP-4 inhibitors such as saxagliptin (SAVOR-TIMI 53) [6], alogliptin (EXAMINE) [7], sitagliptin (TECOS) [8] and linagliptin (CARMELINA, CAROLINA) [9].

In four of these studies it was statistically confirmed that the investigated agents were non-inferior to placebo in regard of primary cardiovascular outcomes (alogliptin, sitagliptin, linagliptin). At the same time, none of the gliptins were beneficial for CVD in the studied patient population (with long-standing DM and CVD).

Metformin, GLP-1 agonists and SGLT2 inhibitors are also considered to have positive effects on cardiovascular system. As for now, there have been no major randomized studies that would assess the effects of metformin on the CVD risk. At the same time. observational and retrospective studies have shown the improvement of cardiovascular prognosis in patients who took metformin for a long time [10]. According to the 2019 ESC Guidelines, metformin should be considered in overweight patients with DM but without CVD or in patients at moderate cardiovascular risk (IIa).

Seven randomized studies have been conducted to investigate the effects of GLP-1 agonists on the cardiovascular outcomes in patients with DM and high cardiovascular risk. It is well known that these agents have some positive effects on some cardiovascular parameters, including the moderate reduction of SAP and weight loss, as well as direct positive effects on heart and blood vessels [11]. Several trials have shown that lixisenatide (ELIXA) [12], exenatide (EXSCEL) [13] and dulaglutide (REWIND) [14] were non-inferior to placebo in regard of primary cardiovascular outcomes which is an indication of positive cardiovascular safety profile. Gradual improvement of outcomes during the treatment can possibly indicate the association of the positive effects with the slowing of atherogenesis.

The best results in regards of cardiovascular safety were shown in SGLT2 trials. This conclusion in based on the results of four randomized trials in patients with DM and high cardiovascular risk. In the EMPA-REG OUTCOME empagliflozin significantly reduced the risk of the composite primary outcome (CV death, non-fatal MI, or non-fatal stroke) compared with placebo, and the reduction was driven mainly by a highly significant reduction in CV death [18]. Positive effects of canagliflozin were shown in the CANVAS and CREDENCE trials. A significant reduction in the composite MACE (CV death, non-fatal MI, or non-fatal stroke) and HF hospitalizations were noted even in patients with very high cardiovascular risk (patients with DM and chronic kidney disease with albuminuria) [19]. DECLARE-TIMI 58 examined the effect of dapagliflozin and revealed no significant reduction of the major MACE. However, dapagliflozin use resulted in the reduced risk of the composite primary out-come (CV death and HF hospitalization). The positive cardiovascular effects of these agents are mostly unrelated to the extent of glucose lowering and occur prior to weight reduction. Rapid and significant reduction in the number of HF hospitalizations in all four studies indicate that the beneficial cardiovascular effects of these agents are more likely the result of their hemodynamic effects (reduced plasma volume, direct effects on cardiac metabolism and function). These effects result in a reduction in HF-associated events [20].

Of note, for the first time the induction monotherapy with SGLT2 or GLP-1 agonists instead of metformin was recommended in patients with T2DM and high/very high cardiovascular risk (the majority of patients). Metformin can be added if the monotherapy is insufficient. SGLT2, GLP-1 agonists, DPP-4 inhibitors, basal insulin and sulfonylureas can be further added in case of persistent hyperglycemia.

The add-on therapy with SGLT-2 inhibitors or GLP-1 agonists with proven beneficial cardiovascular effects is also indicated in the same group of patients (patients with DM and high/very high risk of CVD) who were earlier receiving hypoglycemic agents. In case of insufficient glycemic control one additional agent that has not been used earlier can be added: SGLT2 inhibitor or GLP-1 agonist, DPP-4 inhibitor, basal insulin, sulfonylureas. In patients with DM and high/very high risk of CVD the priority should be given to empagliflozin or liraglutide (IB) as these agents are associated with decreased mortality. As such, GLP-1 agonists and SGLT2 inhibitors are indicated in patients with DM and high/very high cardiovascular risk independently of previous treatment.

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