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Cardiovascular diseases and risk management: the standards in diabetes mellitus 2023 (ADA recommendations). Opinion of the Russian experts

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In early 2023, experts from the American Diabetes Association (ADA) published the Standards of Diabetes Care document in the journal Diabetes Care, which is updated annually as new evidence accumulates. These guidelines aim to improve the diagnosis, treatment and care of patients with diabetes mellitus (DM). One of its sections is devoted to cardiovascular diseases (CVD) and management of the risk of cardiovascular complications. The main aspects of this document and the opinion of Russian experts are presented below.

Keywords: diabetes mellitus, cardiovascular disease, cardiovascular complications.

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Introduction

Cardiovascular diseases (CVD), associated with atherosclerosis (coronary heart disease, cerebrovascular disease, or peripheral arterial disease) – is the leading cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM). The annual cost of CVD management in patients with DM in the United States is approximately $37.3 billion [1].

Numerous studies have demonstrated the effectiveness of controlling individual cardiovascular risk factors in preventing or delaying the development of CVD in DM. In addition, simultaneous control of CVD risk factors has a greater benefit. Therefore, aggressive risk factor modification has led to a reduction in CVD morbidity and mortality in individuals with DM over the past decades [2–4].

Heart failure (HF) is recognized as one of the major causes of mortality in people with DM. Prospective studies have shown that the incidence of hospitalization for HF (adjusted for age and sex) is twice as high in people with diabetes compared to those without diabetes [5, 6].

Cardiovascular diseases and risk management

To prevent and treat both atherosclerosis-related CVD and CHD, risk factors (RFs) should be systematically assessed at least annually in all individuals with diabetes. Important aggravating RFs include: duration of diabetes, obesity/overweight, arterial hypertension (AH), dyslipidemia, smoking, family history of CVD, chronic kidney disease (CKD), and albuminuria.

Therapy using multiple evidence-based approaches in parallel provides additional reductions in the risk of microvascular, renal, neurological and cardiovascular complications. Control of glycemia, blood pressure (BP), and lipid parameters, as well as the incorporation of specific drugs with favorable effects on cardiovascular and renal outcomes (depending on individual differences), are considered key to the overall reduction of the risk of complications of DM.

Cardiovascular complications risk scale

The CVD risk scale (Risk Estimator Plus, USA) is a useful tool for estimating the 10-year risk of cardiovascular complications. The calculation of DM risk is included as a RF, although the duration of the DM or the presence of its complications such as albuminuria are not included. Stratification of CVD risk may help in choosing the therapy. Recently, risk scales and new cardiovascular biomarkers have been developed for risk stratification of patients for secondary prevention, but they are not yet widely used [7, 8].

Arterial hypertension and blood pressure control

AH is common in both type 1 and type 2 DM patients and is a major RF of atherosclerotic cardiovascular disease (ACVD) and microvascular complications [9].

The definition of arterial hypertension

In contrast to Russian and European guidelines, AH is defined as systolic BP ⩾130 mmHg and/or diastolic BP ⩾80 mmHg based on the average of ⩾2 measurements at ⩾2 visits, which is the definition of the American College of Cardiology and the American Heart Association [10]. In individuals with BP ⩾180/110 mmFHg and CVD, the diagnosis of AH can be made in a single visit. If the hypertension is diagnosed, BP control should be performed at every routine office visit and necessarily at home [11, 12], as it is believed that home measurements may correlate better with CVD than office measurements, also by improving adherence to antihypertensive medication [13, 14]. Separate attention is given to the detection of orthostatic hypotension, the presence of which may indicate autonomic neuropathy and require adjustment of BP target values.

Target blood pressure values

The paper analyzes the underlying protocols that compared strategies of "hard" and "soft" control of systolic and diastolic BP: SPRINT (no patients with DM), STER, ACCORD BP, ADVANCE, NOT [15–19]. On the basis of these trials, the experts refer to the goal of antihypertensive therapy in patients with type 1 and type 2 DM as BP < 130/80 mmHg if it can be safely achieved, noting that there are currently no high-quality data to support these values for patients with type 1 DM. The final discussion on BP target values emphasizes the place of a personalized approach based on shared decision-making between physician and patient, with the recommendation not to lower BP <120/80 mmHg because of the risk of adverse events. This strategy is consistent with the opinion of the world's leading expert communities: American College of Cardiology and American Heart Association [9, 10], International

Society of Hypertension [11] and European Society of Cardiology [12].

Pregnancy and arterial hypertension

Approaches to antihypertensive therapy in pregnant women with AH and DM are specified separately: similar to the Russian guidelines, the initiation of therapy in them is justified at BP ⩾140/90 mmHg, and the target values of BP are 110-135/85 mmHg. At the same time, there are no convincing data on the optimal lower limit, but the intensity of therapy should be reduced at BP <90/60 mmHg. This approach is supported by the International Society for the Study of Hypertension in Pregnancy, whose experts recommend a target systolic BP between 110 and 140 mmHg and a target diastolic BP between 80 and 85 mmHg [20].

Treatment with angiotensin converting enzyme inhibitors (ACE inhibitors), angiotensin receptor blockers (ARBs), and spironolactone is prohibited during pregnancy because of the risk of fetotoxicity. These drugs are also undesirable in "individuals with preserved fertile potential" who should be switched to alternative antihypertensive drugs approved for use during pregnancy, namely methyldopa, labetalol and long-acting nifedipine. Hydralazine may be considered as an emergency treatment [16]. Diuretics are not recommended for blood pressure control in pregnancy, but may be used in late pregnancy if needed to control circulatory volume [21, 22]. The American College of Obstetricians and Gynecologists also recommends 7–10 days of postpartum care, including 72 hours in the hospital, for women with gestational hypertension, pre-eclampsia, and pre-eclampsia in the setting of chronic AH. Their long-term follow-up is also warranted due to increased lifelong cardiovascular risk [23].

Lifestyle modification

Lifestyle modification interventions are already recommended for people with BP > 120/80 mmHg and should be continued along with pharmacological BP correction when the AH is diagnosed. These include: weight loss, if necessary; the DASH diet, including reducing sodium (<2300 mg/day) and increasing potassium in the diet; adequate consumption of fruits and vegetables (8–10 servings per day) and non-fatty dairy products (2–3 servings per day); moderate alcohol consumption (no more than 2 servings per day for men and no more than 1 serving per day for women) [24]; and increased physical activity (at least 150 minutes of moderate-intensity aerobic exercise per week) [25].

Traditionally, it is emphasized that lifestyle modification should be discussed in conjunction with goals, taking into account the patient's capabilities, and is an important component of AH treatment due to hypotensive effect, increasing the effectiveness of some antihypertensive drugs, additive interaction with other factors of metabolic and vascular health. The use of the Internet, mobile digital platforms for more active reminders of "healthy behavior" is encouraged, which can be considered as a component of the management of patients with DM, as these interventions enhance the effectiveness of drug therapy for AH [26, 27].

Pharmacological correction

In contrast to Russian and European guidelines for the treatment of AH, this document allows the monotherapy for patients with DM and AH if their BP is between 130/80-160/100 mmHg. Individuals with confirmed office BP ⩾160/100 mmHg in addition to lifestyle modification, should be prescribed with two drugs with proven efficacy in free or fixed combination in a single tablet and should be titrated in a timely manner [28-30].

In contrast to Russian and European recommendations for initial treatment of AH, renin-angiotensin-aldosterone system blockers are not prioritized. ACE inhibitors, BRAs [31, 32], thiazide-like diuretics [33] or dihydropyridine calcium channel blockers [34] can be considered as initial therapy, as all of them have been shown to reduce the risk of cardiovascular events in patients with DM. Administration of an ACE inhibitors or BRAs is suggested as the preferred strategy for the treatment of AH in patients with DM and CHD or a urinary albumin-to-creatinine ratio of 30–299 mg/g, and is strongly recommended if the ratio is greater than 300 mg/g.

However, in the absence of albuminuria, the risk of progression of renal disease is low, and ACE inhibitors, BRAs have not been shown to provide better cardioprotection than thiazide-like diuretics or dihydropyridine calcium channel blockers [35]. Thiazide-like diuretics such as chlorthalidone or indapamide are preferred by experts. In patients treated with an ACE inhibitors, BRA, or diuretic, serum creatinine levels,

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estimated glomerular filtration rate (GFR), and serum potassium levels should be monitored at least annually. Beta-blockers also have their therapeutic niche in this document: they should be prescribed in the presence of previous myocardial infarction (MI), angina pectoris, or chronic heart failure (CHF) with reduced ejection fraction, but in the absence of these conditions their effect on mortality has not been proven [36-38].

Multiple drug therapy is often required to achieve blood pressure targets, especially in the setting of diabetic nephropathy. However, the concomitant use of ACE inhibitors and BRAs or the combination of ACE inhibitors or BRAs with a direct renin inhibitor is contraindicated because of the lack of additional benefit in the prevention of CVD and the increased incidence of adverse events – hyperkalemia, syncope, and acute kidney injury [39-41]. Similar to the clinical guidelines of the world's leading expert communities devoted to the correction of the leading cardiovascular RFs, the need for timely intensification of antihypertensive therapy (dose titration and/or addition of another drug) to overcome therapeutic inertia and achieve target BP values is actualized.

Dosing before bedtime. Although previous analyses of randomized clinical trials have shown benefits of evening versus morning antihypertensive dosing [42, 43], these results have not been replicated in subsequent studies. Therefore, preferential use of antihypertensive drugs at bedtime is not currently recommended [44].

Hyperkalemia and Acute Kidney Injury. Treatment with ACE inhibitors and BRAs may cause acute kidney injury and hyperkalemia, while diuretics may cause hypokalemia or hyperkalemia in addition to acute kidney injury (depending on their mechanism of action) [15, 45]. Detection and treatment of these abnormalities is important because they increase the risk of CVD and death. Therefore, serum creatinine and potassium should be monitored during treatment with an ACE inhibitors, BRA, or diuretic, especially in patients with decreased GFR who are most at risk for hyperkalemia and acute kidney injury [15, 17, 45].

Resistant arterial hypertension

Resistant hypertension is defined as BP ⩾140/90 mmHg despite a therapeutic strategy that includes lifestyle modification, as well as diuretics and two other antihypertensive drugs with complementary mechanisms of action at appropriate doses. That is, the guidelines do not emphasize the need for maximal drug doses. Before diagnosing resistant AH, noncompliance (e.g., due to missed doses, side effects, high cost of treatment), white-coat effect, and secondary hypertension should be excluded. Consequently, patients with secondary AH cannot be considered to have resistant AH.

To achieve BP goals in patients with DM and resistant AH, the addition of mineralocorticoid receptor antagonists (spironolactone, eplerenone) to treatment with an ACE inhibitor or BRA, a thiazide-type diuretic, and a dihydropiridine calcium channel blocker is recommended [44]. Mineralocorticoid receptor antagonists reduce albuminuria in patients with diabetic nephropathy [19, 46, 47], but the risk of hyperkalemia must be considered when adding them to a regimen that includes an ACE inhibitor or BRA. This reaffirms the importance of regular monitoring of serum creatinine and potassium levels and the need to study the long-term results of the use of mineralocorticoid receptor antagonists in the treatment of AH.

Correction of lipid metabolism disorders

Basic principles of lifestyle modification in lipid metabolism disorders

This section is based on the recommendations of the American College of Cardiology and the American Heart Association for the primary prevention of cardiovascular diseases [48]. A Mediterranean-style diet with a reduction in saturated and transfats in foods; increased intake of omega-3 fatty acids, dietary fiber, and plant stanols/sterols (e.g., oatmeal), legumes, and citrus fruits is required. Increased physical activity is also recommended to improve lipid profiles and reduce the risk of developing ACVD in people with DM.

Along with the lifestyle modification, optimization of glycemic control is recommended in patients with elevated triglycerides (⩾150 mg/dL [1.7 mmol/L]) and/or low high-density lipoprotein (HDL) cholesterol (<40 mg/dL [1.0 mmol/L] for men, < 50 mg/dL [1.3 mmol/L] for women. Glycemic control may have a beneficial effect on plasma lipid levels, particularly in patients with very high triglyceride levels and poor glycemic control.

Weight loss is recommended in obese or overweight individuals (if necessary), which, along with increased physical activity, may reduce the impact

of risk factors on the development of CVD in some patients. Dietary interventions should be tailored to each patient's age, pharmacological treatment, lipid levels, and overall health.

Particular features of lipid profile control different from European guidelines

In adults with DM, it is recommended that the lipid profile of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides be measured at the time of diagnosis at the initial physical examination and at least every 5 years in patients younger than 40 years.

In younger individuals with a longer disease course (e.g., type 1 DM onset at a young age), more frequent lipid profile monitoring may be appropriate. The lipidogram should be checked immediately before starting statin therapy. Once the patient starts taking statins, LDL cholesterol levels should be assessed 4–12 weeks after initiation of therapy (in Russian and European guidelines, after 4–8 weeks of therapy), as well as after each dose change and on an individual basis (e.g., to monitor drug absorption and efficacy). If LDL cholesterol levels do not change despite medication, clinical evaluation is recommended to determine the need for and timing of lipid profile measurements. The highly variable LDL cholesterol-lowering response to statins is poorly understood in individual patients. Clinicians should attempt to adjust doses or find alternatives to statins when side effects occur. There is an evidence of benefit even of the very low doses of statins, much lower than those usually recommended.

Treatment with statins for primary prevention

This section is presented according to the guidelines of American endocrinologists [49–51]. For people with diabetes aged 40–75 years without ACVD, it is recommended to use moderate-intensity statin therapy in addition to lifestyle changes (in contrast to the Russian and European recommendations, risk levels and risk scales are not used, but division into age groups). For people with diabetes aged 20–39 years with additional ACVD RFs, it is recommended to start statin therapy in addition to lifestyle changes.

For people with DM aged 40–75 years at increased risk of CVD, including those with one or more ACVD RFs, it is recommended that high-intensity statin therapy be used to reduce LDL cholesterol by ≥ 50 % of baseline and achieve a target LDL cholesterol level of <1.8 mmol/L.

For people with DM aged 40–75 years who are at increased cardiovascular risk, especially those with multiple ACVD RFs and LDL cholesterol levels ≥1.8 mmol/L, the addition of ezetimibe or the proprotein convertase inhibitor subtilisin/kexin type 9 (PCSK9) to the maximum tolerated dose of a statin may be appropriate. In patients with DM older than 75 years who are already receiving statin therapy, it is reasonable to continue such treatment. In people with DM older than 75 years, it may be appropriate to initiate moderate-intensity statin therapy after discussing the potential benefits and risks. Statin therapy is contraindicated during pregnancy.

Statin treatment for secondary prevention

High-intensity statin therapy should be added to lifestyle interventions for people of all ages with DM and ACVD.

High-intensity statin therapy is recommended for people with DM and ACVD to reduce LDL cholesterol by ≥50 % from baseline and achieve a target LDL cholesterol level of <1.4 mmol/L. The addition of ezetimibe or a PCSK9 inhibitor with proven efficacy is recommended if this goal is not achieved with the maximum tolerated dose of a statin.

People who cannot tolerate the maximum doses of statins should be prescribed the maximum tolerated doses of these drugs.

Accordingly, statins are the drugs of choice for LDL cholesterol lowering and cardioprotection: high-intensity statin therapy reduces LDL cholesterol by approximately ≥50 % and moderate-intensity statin therapy reduces LDL cholesterol by 30–49 % (Table 1). Treatment with low-dose statins is not usually recommended for people with DM, but sometimes it is the only possible dose of statins that a patient can tolerate. In patients who cannot tolerate statin therapy at the desired intensity, the maximum tolerated dose of statins should be used.

Moderate-intensity statin therapy is recommended for primary prevention in patients aged ≥40 years, although high-intensity therapy should be considered in the context of additional ACVD risk factors. Because it is often difficult in clinical practice to establish baseline LDL cholesterol levels prior to initiating statin therapy, it is recommended that these patients focus

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Table 1

Lowering cholesterol levels with statin therapy

High-intensity statin therapy (reduces LDL cholesterol by ⩾ 50 %)	Moderate-intensity statin therapy (reduces LDL cholesterol by 30 – 49 %)
Atorvastatin 40 – 80 mg	Atorvastatin 10 – 20 mg
Rosuvastatin 20 – 40 mg	Rosuvastatin 5 – 10 mg
	Simvastatin 20 – 40 mg
	Pitavastatin 1 – 4 mg

on a target LDL cholesterol level of <1.8 mmol/L rather than a percentage reduction in LDL cholesterol. In these individuals, it may also be appropriate to add ezetimibe or a PCSK9 inhibitor to maximally tolerated statin therapy if needed to reduce LDL cholesterol by ⩾ 50 % and achieve the recommended target LDL cholesterol level of <1.8 mmol/L. Moderate intensity statin therapy is recommended for people with DM aged ⩾ 75 years. However, in this population, the risk-benefit ratio of treatment should be regularly reassessed and the dose reduced if necessary.

Recommendations for age group under 40 years and/or with type 1 diabetes mellitus

Patients younger than 40 years of age have a lower risk of developing CVD over a 10-year period, but they have a high lifetime risk of developing CVD and MI, stroke, or death from CVD. It is recommended that people younger than 40 years of age and/or those with type 1 DM with other comorbidities discuss the relative benefits and risks of treatment with their physician and consider the use of moderate-intensity statin therapy [52].

Patients with atherosclerotic cardiovascular diseases

High-intensity statin therapy is recommended for all people with DM and ACVD to reduce LDL cholesterol by ⩾50 % of baseline and achieve a target LDL cholesterol level of <1.4 mmol/L. If this goal is not achieved with maximally tolerated statin therapy, the addition of ezetimibe or a PCSK9 inhibitor is recommended. Evidence supporting progressively lower LDL cholesterol targets in people with DM and established CVD comes from several large randomized trials evaluating the benefits of adding non-statin drugs to statin therapy. Each study found a significant benefit in the reduction of ACVD events that was directly related to the degree of further reduction in LDL cholesterol. These large trials included significant numbers of participants with DM and prespecified rates of cardiovascular outcomes in people with and without DM. The decision to add a non-statin drug should be made after the physician and patient have discussed the benefits, safety, and costs of combination therapy [53–56].

Combination therapy to lower low-density lipoprotein cholesterol levels

Overall, the addition of ezetimibe resulted in a relative reduction of 6.4 % and an absolute reduction of 2 % in the risk of major adverse cardiovascular events (atherosclerotic cardiovascular events), according to the guideline authors. The magnitude of the benefit was directly proportional to the change in LDL cholesterol, which averaged 1.8 mmol/L in the statin group and 1.4 mmol/L in the combination therapy group. In patients with DM (27 % of study participants), the combination of moderate-intensity doses of simvastatin (40 mg) and ezetimibe (10 mg) showed a significant reduction in the risk of major adverse cardiovascular events, with an absolute risk reduction of 5 % and a relative risk reduction of 14 % compared with simvastatin monotherapy at a dose of 40 mg.

The effect of PCSK9 inhibition on the ACVD outcomes identified in these guidelines was evaluated in the FOURIER trial, which enrolled 27564 high-risk patients with prior ACVD who were on maximum tolerated doses of statins. Evolocumab reduced LDL cholesterol levels by 59 %. At a median follow-up of 2.2 years, the combined outcome of CVD death, MI, stroke, angina hospitalization or revascularization was reported in 11.3 % of patients compared to 9.8 % in the placebo and evolocumab groups (15 % relative risk reduction; p<0.001). The composite of cardiovascular death, MI or stroke was reduced by 20 % (p<0.001). Importantly, similar benefits were observed in a pre-specified subgroup of people with DM comprising 11031 patients (40 % of the study population).

In another study, ODYSSEY OUTCOMES, 18924 patients (28.8 % of whom had DM) with a recent acute coronary syndrome were randomized to receive the PCSK9 inhibitor alirocumab or placebo every 2 weeks on top of maximum tolerated statin therapy. The

dose of alirocumab was titrated from 75 to 150 mg to achieve LDL cholesterol levels of 25 to 50 mg/dL. At a median follow-up of 2.8 years, the combination of alirocumab and statins resulted in a greater absolute reduction in the incidence of the primary endpoint in people with DM (by 2.3%) than in people with pre-diabetes (by 1.2%) or normoglycemia (by 1.2%).

In addition to monoclonal antibodies targeting PCSK9, a small interfering RNA therapy, inclisiran, has been developed and has recently become available in the United States and Russia. Treatment with inclisiran involves less frequent dosing compared to monoclonal antibodies and has been administered at day 1, day 90 and every 6 months in studies. In the ORION-10 study, 47.5% of patients in the inclisiran group and 42.4% of patients in the placebo group, and in the ORION-11 study, 36.5% and 33.7% of patients, respectively, had DM. A prespecified cardiovascular endpoint, which includes death from heart attack, cardiac arrest, non-fatal MI or stroke, was observed in 7.4% of patients in the inclisiran group and 10.2% of patients in the placebo group in ORION-10 and 7.8% and 10.3%, respectively, in ORION-11.

Severe hypertriglyceridemia (fasting triglyceride levels ≥5 mmol/L and especially >10 mmol/L) requires pharmacologic therapy (fibrates and/or fish oil – omega-3 polyunsaturated fatty acids) and reduction of dietary fat to reduce the risk of acute pancreatitis. Moderate to high intensity statin therapy should also be used when indicated to reduce the risk of cardiovascular events. In people with moderate hypertriglyceridemia, lifestyle modification, treatment of secondary risk factors, and avoidance of medications that may increase triglyceride levels are recommended [57].

Management of patients with hypertriglyceridemia

The REDUCE-IT trial enrolled 8179 adults receiving statin therapy with moderately elevated triglyceride levels (1.4–4.9 mmol/L, median baseline 2.16 mmol/L) who had established CVD (secondary prevention) or DM plus at least one other CVD risk factor (primary prevention) [58]. Patients were randomized to receive icosapentetil (omega-3 polyunsaturated fatty acid) at a dose of 4 g/day (2 g twice daily with meals) versus placebo. A 25% relative risk reduction ($p<0.001$) was achieved for the primary endpoint consisting of CVD death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina. This risk reduction while taking icosapentetil was observed in people with or without DM. The combination of cardiovascular death, non-fatal MI or non-fatal stroke was reduced by 26% ($p<0.001$). It should be noted that similar data on the efficacy of other omega-3 polyunsaturated fatty acids are not available, and the results of the REDUCE-IT study should not be extrapolated to other products.

Combination therapy with statins and fibrates does not improve ACVD outcomes and is generally not recommended (in contrast to Russian and European recommendations). Combination therapy (statins and fibrates) is associated with an increased risk of abnormal transaminase levels, myopathy, and rhabdomyolysis. The risk of rhabdomyolysis is greater with higher doses of statins and renal failure and appears to be higher when statins are combined with gemfibrozil (compared with fenofibrate).

Risk of diabetes mellitus when using statins

Although the use of statins is associated with the risk of developing DM, the reduction in the incidence of cardiovascular events with statins far outweighs the risk of DM, even in patients at the highest risk of developing DM. A meta-analysis of 13 randomized trials of statins involving 91,140 participants showed that the odds ratio for a new diagnosis of DM was 1.09, meaning that, on average, treatment with statins for 4 years in 255 patients resulted in one additional case of DM while preventing 5.4 vascular events in these 255 patients [59].

Concerns that statins or other hypolipidemic agents may cause cognitive dysfunction or dementia are not currently supported by evidence and should not prevent their use in individuals with DM and high risk of the ACVD [60].

The use of antiplatelet drugs

There is a large base of evidence that the benefits of using aspirin for secondary prevention in people with documented CVD far outweigh the risks [61]. Aspirin has been shown to be effective in reducing CVD and mortality in high-risk patients with a history of MI or stroke (secondary prevention) [62].

There is currently no convincing evidence to support the use of a specific dose of aspirin. However, the average daily doses used in most clinical trials in patients with DM ranged from 50 to 650 mg, but were

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usually in the range of 100 – 325 mg/day. Consequently, the lowest possible dose of aspirin is appropriate to reduce side effects, primarily the risk of major bleeding [63]. For patients with DM and high/very high cardiovascular risk, European experts recommend the use of aspirin at a dose of 75 – 100 mg/day [62].

In the ADAPTABLE trial involving patients with confirmed CVD, 38 % of whom had DM, there were no significant differences in the incidence of cardiovascular events or major bleeding between patients treated with 81 mg or 325 mg of aspirin daily [64].

Although platelet dysfunction is present in individuals with DM, it is unclear what effect, if any, this finding has on the dose of aspirin required for cardioprotection in DM. There are many alternative pathways of platelet activation that are independent of thromboxane A2 and therefore unaffected by aspirin [65]. "Aspirin resistance" has been described in DM using a variety of ex vivo and in vitro methods (platelet aggregometry, thromboxane B2 measurement) [66], but impaired response to aspirin in DM patients has not been confirmed in other studies [67]. It has been shown that more frequent aspirin dosing may reduce platelet reactivity in people with DM [68]; however, these observations alone are not sufficient to recommend the use of higher doses of aspirin in this group at this time. A meta-analysis hypothesized that the efficacy of low-dose aspirin is reduced in individuals with a body weight >70 kg [69]. However, the ASCEND trial found a benefit of low-dose aspirin in individuals of this weight, contradicting this hypothesis [70]. According to the ADA guidelines, aspirin doses of 75 – 162 mg/day are optimal [71].

Thus, aspirin therapy at a dose of 75 – 162 mg/day should be used as a secondary prevention strategy in patients with a history of DM and ACVD [71].

In recent years, other antiplatelet agents, particularly clopidogrel, have been studied as alternatives to aspirin [12]. However, there is evidence that clopidogrel is less effective than aspirin in patients with DM [73].

At the same time, clopidogrel at a dose of 75 mg/day is recommended in documented aspirin allergy in patients with DM and ACVD [71].

The use of dual antiplatelet therapy has an undoubted advantage over aspirin monotherapy in patients with acute coronary syndrome and percutaneous coronary intervention. Thus, the use of a P2Y12 receptor antagonist in combination with aspirin is reasonable for at least 1 year in patients who have had an acute coronary syndrome and may provide benefit beyond this period.

Trial results support the use of either ticagrelor or clopidogrel if percutaneous coronary intervention was not performed, and clopidogrel, ticagrelor, or prasugrel if it was performed [74]. In patients with DM and a history of MI (1–3 years old), the addition of ticagrelor to aspirin significantly reduced the risk of recurrent ischemic events, including cardiovascular death and death due to CHD [75]. Similarly, the addition of ticagrelor to aspirin reduced the risk of ischemic cardiovascular events compared with aspirin alone in subjects with DM and stable CHD [76, 77]. However, a higher incidence of major bleeding, including intracranial hemorrhage, was observed with dual antiplatelet therapy, which requires a more balanced approach (careful consideration of bleeding risk) 1 year after acute coronary syndrome.

Therefore, the ADA expert recommendation that dual antiplatelet therapy (low-dose aspirin plus a P2Y12 receptor inhibitor) is reasonable for 1 year after acute coronary syndrome and may be of benefit beyond this period seems most reasonable [71].

The net clinical benefit (effect on the sum of ischemic and hemorrhagic complications) is higher with ticagrelor therapy in patients with a history of percutaneous coronary intervention, whereas no such benefit is observed in patients without such intervention [77].

In this context, according to the ADA Expert Recommendation, individuals with a history of coronary intervention, high coronary risk, and low bleeding risk should consider long-term dual antiplatelet therapy to prevent major adverse cardiovascular events [71].

However, early discontinuation of aspirin compared with continuing dual antiplatelet therapy after coronary stenting may reduce the risk of bleeding without a corresponding increase in the risk of mortality and ischemic events, as shown in an analysis of a cohort of patients with DM included in the TWILIGHT trial and in a recent meta-analysis [78, 79].

In recent years, a combination of aspirin and low-dose rivaroxaban has been considered as a pharmacological approach to reduce cardiovascular risk in individuals with stable coronary heart disease and/or peripheral arterial disease. In the COMPASS trial, which enrolled 27,395 patients with documented CHD and/or PAD, aspirin 100 mg once daily plus ri-

varoxaban 2.5 mg twice daily was superior to aspirin 100 mg once daily plus placebo in reducing the risk of cardiovascular ischemic events, including major adverse limb ischemic events. The absolute benefit of combination therapy was greater in a group of 10,341 study participants with DM [80, 81]. A similar treatment strategy was evaluated in the VOYAGER PAD Vascular Outcomes Study [82], in which 6564 patients with PAD undergoing revascularization were randomized to rivaroxaban (2.5 mg twice daily) plus aspirin or placebo plus aspirin. In the rivaroxaban group, there was a significant reduction in the incidence of ischemic cardiovascular complications, including major adverse events in the lower extremities. However, there was an increased risk of major bleeding when rivaroxaban was added to aspirin therapy in both COMPASS and VOYAGER PAD. These data suggest that patients should be carefully selected for combination therapy with aspirin and rivaroxaban, as supported by the following ADA expert recommendation.

In individuals with stable coronary and/or peripheral arterial disease and low risk of bleeding, combination therapy with aspirin plus low-dose rivaroxaban should be considered to prevent severe limb and cardiac ischemic events [71].

Current evidence precludes the recommendation of aspirin and other antiplatelet agents for primary prevention in individuals at low risk of CVD (e.g., men and women aged <50 years with DM without other major CVD risk factors), because the risk of bleeding is likely to outweigh the small benefit [83]. Previous randomized controlled trials of aspirin in people with DM have consistently failed to demonstrate a significant reduction in CVD risk. This calls into question the efficacy of aspirin for primary prevention in people with DM, although some sex differences have been suggested [84-86].

In the ASCEND trial, which included 15,480 participants with DM but without documented CVD, patients were randomized to receive aspirin at a dose of 100 mg daily or placebo [70]. The primary efficacy endpoints were: vascular death, MI, or stroke/transient ischemic attack. During a mean follow-up of 7.4 years, there was a significant 12% reduction in the rate of the primary efficacy endpoint (p=0.01), but there was a significant 1.3-fold increase in the rate of major bleeding in the aspirin group (p=0.003), and this increase was associated with gastrointestinal and other extracranial bleeding. No significant differences in outcomes were observed according to sex, body weight, duration of DM, and baseline CVD risk. Two other large randomized trials of aspirin for primary prevention in people without DM (ARRIVE) [87] and in elderly patients (ASPREE) [88], which included 11% of patients with DM, found no benefit of aspirin with respect to the primary efficacy endpoint of increased risk of bleeding.

Analysis of the available data may suggest that aspirin has a moderate effect on ischemic vascular events, with an absolute reduction in their incidence depending on the risk of CVD. The main adverse effect of aspirin is an increased risk of gastrointestinal bleeding, which may reach 5 cases per 1000 patients per year in real-world practice. However, in adults with a CVD risk > 1% per year, the number of cases prevented by aspirin is equal to the number of drug-induced bleeding events, although these complications do not have the same impact on long-term health [89].

Therefore, the use of aspirin for primary prevention of CVD should be carefully justified and is generally not recommended. Aspirin may be considered in the context of high cardiovascular risk with low bleeding risk [90–93], but generally not in the elderly. In people over 70 years of age (with or without DM), the risks of aspirin use appear to outweigh the benefits [70, 88]. Aspirin use is generally contraindicated in patients under 21 years of age because of the associated risk of Reye's syndrome. The willingness of patients to take aspirin long-term should also be considered [94].

In this context, the recommendation of the ADA experts that aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in patients with DM at increased cardiovascular risk, after a comprehensive discussion with the patient about the benefits compared with a comparable increased risk of bleeding, is justified [71].

Specifics of managing patients with diabetes mellitus and cardiovascular diseases

Cardiologic testing

Candidates for advanced or invasive cardiac testing are DM patients who have: 1) typical or atypical cardiac symptoms, and 2) resting electrocardiogram

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(ECG) abnormalities. A stress ECG with or without echocardiographic imaging may be used as an initial test. In adults with DM aged ≥40 years, measurement of coronary artery calcium is also appropriate for cardiovascular risk assessment. Pharmacologic stress echocardiography or nuclear imaging should be considered in individuals with DM in whom abnormal resting ECG changes preclude exercise testing (e.g., left bundle branch block or ST-T abnormalities). Pharmacologic stress echocardiography or nuclear imaging may also be used in detrained individuals who require exercise testing.

Screening of asymptomatic patients

The screening of asymptomatic patients at high risk for ACVD is not recommended [95], partially because these patients should already be receiving intensive medical therapy, a treatment that provides similar benefits to invasive revascularization [96, 97]. In prospective studies, coronary calcium measurement has been hypothesized to be an independent predictor of cardiovascular complications in people with DM, superior to the assessment used in the UKPDS and Framingham study populations [98-100]. However, a randomized observational study demonstrated a lack of clinical benefit from routine screening of asymptomatic individuals with type 2 DM and a normal ECG [101]. Despite imaging evidence of impaired myocardial perfusion in more than one in five patients, the incidence of adverse cardiac outcomes was similar in screened and unscreened patients. Therefore, non-selective screening is not cost-effective. Studies have shown that a risk factor-based approach to the initial diagnostic evaluation and follow-up of patients with CHD does not help to determine which people with type 2 DM will have silent myocardial ischemia on screening tests [102, 103].

Any benefit of newer noninvasive coronary artery disease screening modalities, such as CT calcinosis assessment and computed tomographic angiography, in asymptomatic people with DM remains uncertain in terms of identifying patient subgroups for different treatment strategies. Asymptomatic people with DM and a higher burden of coronary heart disease are at higher risk of future cardiac events [98, 104, 105], and additional imaging tests may provide justification for intensification of treatment and/or lead to informed patient decision making, readiness to initiate therapy, and active participation in therapy. While screening methods for coronary artery pathology, such as coronary calcium scoring, may improve cardiovascular risk assessment in people with type 2 DM [106], their routine use is associated with radiation exposure and may lead to unnecessary invasive testing, such as coronary angiography, and revascularization procedures. The final balance of benefits, costs, and risks of this approach in asymptomatic patients remains controversial, especially in the current setting of aggressive control of ACVD risk factors.

Lifestyle modification and pharmacotherapy

Intensive lifestyle modifications, focusing on weight loss by reducing caloric intake and increasing physical activity, as in the Look AHEAD trial, can be considered to improve glycemic control, maintain fitness, and correct some ACVD risk factors [107]. Patients at increased risk of ACVD should take statins, ACE inhibitors or BRAs if they have AH, and possibly aspirin if there are no contraindications to these drugs. Because of the clear benefits of ACE inhibitors or BRAs in people with DM, kidney disease, or AH, these drugs are recommended for BP lowering in people with established ACVD (especially CHD) [108-110]. In people with type 2 DM and CHD, treatment with finerenone should be considered to reduce the risk of adverse cardiovascular outcomes and progression of CHD [111-114]. Beta-blockers should be used in people with angina pectoris or CHF with reduced ejection fraction and within 3 years of MI in patients with preserved left ventricular ejection fraction [115, 116].

Glucose-lowering therapy and cardiovascular outcomes

In 2008, the U.S. Food and Drug Administration (FDA) issued a directive for drug manufacturers to evaluate cardiovascular outcomes in studies of all new type 2 diabetes medications due to concerns about increased cardiovascular risk. Previously approved drugs for the treatment of type 2 DM were not subject to such a safety assessment. Recently published studies have provided additional data on cardiovascular and renal outcomes in people with type 2 DM and cardiovascular disease or high cardiovascular risk (Tables 2, 3).

Studies of cardiovascular outcomes with all dipeptidyl peptidase-4 inhibitors have failed to show a cardiovascular benefit of these drugs compared with placebo. The CAROLINA trial showed similar efficacy

Table 2

Trial results, regarding the cardiovascular safety of SGLT-2 inhibitors

Trial	EMPA-REG OUTCOME (n=7020)	CANVAS Program (n=10 142)	DECLARE-TIMI 58 (n=17 160)	CREDENCE (n=4401)	DAPA-CKD (n=4304; T2DM n = 2906)	VERTIS CV (n=8246)
Intervention	Empagliflozin/ placebo	Canagliflozin/ placebo	Dapagliflozin/ placebo	Canagliflozin/ placebo	Dapagliflozin/ placebo	Ertugliflozin/ placebo
Started/Ended	2010/2015	2009/2017	2013/2018	2017/2019	2017/2020	2013/2020
Primary endpoint	3-component MACE 0.86 (0.74 – 0.99)	3-component MACE 0.86 (0.75 – 0.97)	3-component MACE 0.93 (0.84 – 1.03) Cardiovascular death or hospitalization due to HF 0.83 (0.73 – 0.95)	Terminal CKD. Creatinine doubling or death due to renal or cardiovascular outcomes 0.70 (0.59 – 0.82)	≥50 % GFR reduction. Terminal CKD. Creatinine doubling or death due to renal or cardiovascular outcomes 0.61 (0.51 – 0.72)	3-component MACE 0.97 (0.85 – 1.11)
Cardiovascular death	0.62 (0.49 – 0.77)	0.87 (0.72 – 1.06)	0.98 (0.82 – 1.17)	0.78 (0.61 – 1.00)	0.81 (0.58 – 1.12)	0.92 (0.77 – 1.11)
Myocardial infarction	0.87 (0.70 – 1.09)	0.89 (0.73 – 1.09)	0.89 (0.77 – 1.01)	–	–	1.04 (0.86 – 1.26)
Stroke	1.18 (0.89 – 1.56)	0.87 (0.69 – 1.09)	1.01 (0.84 – 1.21)	–	–	1.06 (0.82 – 1.37)
Hospitalization due to HF	0.65 (0.50 – 0.85)	0.67 (0.52 – 0.87)	0.73 (0.61 – 0.88)	0.61 (0.47 – 0.80)	–	0.70 (0.54 – 0.90)
Hospitalization due to unstable angina	0.99 (0.74 – 1.34)	–	–	–	–	–
All-cause mortality	0.68 (0.57 – 0.82)	0.87 (0.74 – 1.01)	0.93 (0.82 – 1.04)	0.83 (0.68 – 1.02)	0.69 (0.53 – 0.88)	0.93 (0.80 – 1.08)

Table 3

Trial results, regarding the cardiovascular safety of SGLT-2 inhibitors in HF patients with preserved and reduced left ventricular ejection fraction

Trial	DAPA-HF (n=4744; 1983 with T2DM)	EMPEROR-Reduced (n=3730; 1856 with T2DM)	EMPEROR-Preserved (n=5988; 2938 with T2DM)	DELIVER (n=6263; 2807 with T2DM)
Intervention	Dapagliflozin/ placebo	Empagliflozin/ placebo	Empagliflozin/ placebo	Dapagliflozin/ placebo
Inclusion criteria	NYHA class II – IV HF and LVEF ≤40 %, with or without T2DM	NYHA class II – IV HF and LVEF ≤40 %, with or without T2DM	NYHA class II – IV HF and LVEF ≤40 %, with or without T2DM	NYHA class II – IV HF and LVEF ≤40 %, with or without T2DM
Started/Ended	2017/2019	2017/2020	2017/2020	2018/2022
Primary endpoint	HF decompensation or cardiovascular death 0.74 (0.65 – 0.85)	Cardiovascular death or hospitalization due to HF 0.75 (0.65 – 0.86)	Cardiovascular death or hospitalization due to HF 0.79 (0.69 – 0.90)	HF decompensation or cardiovascular death 0.82 (0.73 – 0.92)
Secondary endpoint	Cardiovascular death или Hospitalization due to HF 0.75 (0.65 – 0.85)	All hospitalizations due to HF 0.70 (0.58 – 0.85) Average decrease in GFR 1.73 (1.10 – 2.37)	All hospitalizations due to HF (first and repeated) 0.73 (0.61 – 0.88) GFR decrease level (– 1.25 vs – 2.62 ml/ min/1.73m^2; p<0.001)	Total number of cases of HF decompensation and cardiovascular death 0.77 (0.67 – 0.89) Changes in KCCQ TSS after 8 months 1.11 (1.03 – 1.21) Average change 2.4 (1.5 – 3.4) All-cause mortality 0.94 (0.83 – 1.07)
Cardiovascular death	0.82 (0.69 – 0.98)	0.92 (0.75 – 1.12)	0.91 (0.76 – 1.09)	0.88 (0.74 – 1.05)
Hospitalization due to HF	0.70 (0.59 – 0.83)	0.69 (0.59 – 0.81)	0.73 (0.61 – 0.88)	0.77 (0.67 – 0.89)
All-cause mortality	0.83 (0.71 – 0.97)	0.92 (0.77 – 1.10)	1.00 (0.87 – 1.15)	0.94 (0.83 – 1.07)

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of the DPP-4 inhibitor linagliptin and the sulfonylurea derivative glimepiride in influencing cardiovascular outcomes, despite a lower incidence of hypoglycemia in the linagliptin treatment group [117]. However, trials of other new treatments for type 2 DM have had mixed results.

Studies of sodium-glucose cotransporter type 2 inhibitors

In the randomized EMPA-REG OUTCOME trial in patients with type 2 DM and cardiovascular diseases, the sodium-glucose cotransporter type 2 (SGLT-2) inhibitor empagliflozin reduced the risk of the adverse outcomes (MI, stroke, and cardiovascular death) by 14% (p=0.04) and cardiovascular mortality by 38% (p<0.001) compared to placebo [118]. Results from CANVAS, a research program on the SGLT-2 inhibitor canagliflozin, showed a significant reduction in the risk of the adverse outcomes (cardiovascular death, MI or stroke) compared with placebo. However, there was an increased risk of lower limb amputation in the canagliflozin group [119]. In the CREDENCE study in patients with type 2 DM and CKD, the canagliflozin group had a reduced risk of sum of end-stage kidney disease, doubling of serum creatinine, or death from renal or cardiovascular causes compared with placebo. In this study, there was no significant increase in lower extremity amputations, fractures, acute renal failure or hyperkalemia with canagliflozin compared to placebo. However, an increased risk of diabetic ketoacidosis was observed in the canagliflozin group compared to placebo [120]. The results of the randomized DECLARE-TIMI 58 trial in patients with type 2 DM with documented ACVD (40% of participants) or multiple risk factors met the defined criteria of no less efficacy than placebo with respect to major adverse cardiovascular events, but did not show a reduction in their incidence. The reduced risk of cardiovascular death or hospitalization for HF decompensation in the dapagliflozin group compared with placebo reflected a lower incidence of hospitalization due to HF, with no difference in the risk of cardiovascular death between groups [121]. In the DAPA-CKD study in patients with or without CKD and type 2 DM, the risk of the composite of adverse outcomes (sustained reduction in GFR of at least 50%, end-stage CKD, or death from renal or cardiovascular causes) was significantly reduced in the dapagliflozin group compared with the placebo group [122]. In the VERTIS CV study, the SGLT-2 inhibitor ertugliflozin was equivalent to placebo in its effect on the risk of major adverse cardiovascular outcomes in patients with type 2 DM and documented ACVD. In addition, ertugliflozin reduced the risk of hospitalization due to HF, which is consistent with findings from studies of other SGLT-2 inhibitors [123]. The SGLT-1 and SGLT-2 inhibitor sotagliflozin, which is not currently approved by the FDA in the United States, reduced the cumulative incidence of adverse events (death from cardiovascular causes, hospitalization, or need for acute HF decompensation treatment) in the SCORED trial in people with type 2 DM, CKD, and other cardiovascular risk factors. Side effects of sotagliflozin were similar to those observed with other SGLT-2 inhibitors, but included an increased incidence of diarrhea associated with SGLT-1 inhibition [124].

Studies of glucagon-like peptide-1 receptor agonists

In large randomized trials involving patients with type 2 DM, the glucagon-like peptide-1 (GLP-1) receptor agonists liraglutide in LEADER [125], semaglutide in SUSTAIN-6 [126], and dulaglutide in REWIND [127] were shown to reduce the risk of cardiovascular death, non-fatal MI, or non-fatal stroke compared with placebo. The oral form of semaglutide in the randomized PIONEER trial [128], albiglutide in Harmony Outcomes [129], lixisenatide in ELIXA [130], and exenatide in EXSCEL [131] were not superior to placebo in affecting the sum of these adverse outcomes. Currently, the treatment with SGLT-2 inhibitors (empagliflozin, canagliflozin, dapagliflozin) and GLP-1 receptor agonists (liraglutide, semaglutide, and dulaglutide) can significantly reduce the risk of cardiovascular events in people with type 2 DM. According to meta-analyses, drugs in these two classes can comparably reduce the risk of major adverse cardiovascular complications in people with type 2 DM and known ACVD [132, 133]. SGLT-2 inhibitors also reduce the risk of hospitalization due to HF decompensation and progression of kidney disease in people with known ACVD or its multiple risk factors or CKD with albuminuria [134, 135]. Therefore, in patients with type 2 DM and ACVD, multiple risk factors for ACVD, or diabetic nephropathy, SGLT-2 inhibitors with proven efficacy are recommended to reduce the risk of major adverse cardiovascular events and/or hospitalization due to HF decompensation. In type 2 DM patients with

ACVD or multiple ACVD risk factors, GLP-1 receptor agonists with proven efficacy are recommended to reduce the risk of major adverse cardiovascular events. The combined use of SGLT-2 inhibitors and GLP-1 receptor agonists may provide additional improvements in cardiovascular and renal outcomes [136].

Glucose-lowering therapy and heart failure

The common co-occurrence of type 2 DM and HF is characterized by increased morbidity and mortality, requiring appropriate choice of glucose-lowering agents to improve outcomes. Thiazolidinediones increase the risk of developing HF and should be avoided in people with symptomatic HF [137]. Observational studies in people with type 2 DM and HF have not shown a negative effect of metformin on the outcomes [138]. Despite the lack of relevant randomized trials, metformin can be used to treat hyperglycemia in people with stable HF as long as renal function remains within the recommended range for its use. The dipeptidyl peptidase-4 inhibitor saxagliptin increased the risk of hospitalization due to HF decompensation compared with placebo in the randomized SAVOR-TIMI 53 trial [139]. However, other drugs in this class in cardiovascular outcomes trials – alogliptin in EXAMINE, sitagliptin in TECOS, and linagliptin in CARMELINA – did not have this effect [137]. Trials of the GLP-1 receptor agonists lixisenatide, liraglutide, semaglutide, exenatide, albiglutide, and dulaglutide did not show an increased risk of hospitalization for HF compared to placebo [137].

The use of SGLT-2 inhibitors in patients with type 2 DM was associated with a reduced incidence of hospitalization due to HF compared with placebo in the randomized trials of empagliflozin (EMRA-REG OUTCOME) [118], canagliflozin (CANVAS) [119] and dapagliflozin (DECLARE-TIMI 58) [121]. In patients with New York Heart Association (NYHA) class II – IV CHF and an ejection fraction ⩽40 %, dapagliflozin in the DAPA-HF trial [140] and empagliflozin in the EMPEROR-Reduced trial [141] reduced the risk of cardiovascular death or hospitalization due to CHF decompensation compared with placebo. In patients with NYHA class II – IV CH and an ejection fraction > 40 %, empagliflozin in the randomized EMPEROR-Preserved trial [142] and dapagliflozin in the DELIVER significantly reduced the risk of cardiovascular death or hospitalization due to HF [143]. Approximately half of the participants in these trials had DM, but the presence of DM did not affect the reported outcomes. A meta-analysis of these four trials of SGLT-2 inhibitors, supplemented by the SOLOIST-WHF data using sotagliflozin, showed a reduced risk of cardiovascular death or hospitalization due to HF, cardiovascular death, first hospitalization due to HF, and all-cause mortality in a wide range of patients with HF, supporting their emerging role as first-line therapy for HF regardless of ejection fraction and concomitant therapy [144].

In patients with type 2 DM and diagnosed HF with reduced (<40 %), moderately reduced (41 – 49 %), or preserved (⩾50 %) ejection fraction, treatment with SGLT-2 inhibitors is recommended to reduce the risk of HF progression and cardiovascular death because of their proven benefit in this patient population. In addition, SGLT-2 inhibitors are recommended in this patient population to reduce symptoms and physical limitations and to improve quality of life [145-147]. The observed benefits likely represent a class effect of SGLT-2 inhibitors, are not related to glycemic lowering, and are similar in patients with and without type 2 DM and HF.

Finerenone in patients with type 2 diabetes mellitus and chronic kidney disease

People with DM have an increased risk of CKD, which also increases the cardiovascular risk. The selective nonsteroidal mineralocorticoid receptor antagonist finerenone improved CKD outcomes in the randomized FIDELIO-DKD trial in people with stage 3 or 4 CKD, severe albuminuria, and type 2 DM [148]. In the FIGARO-DKD trial in patients with diabetic nephtopathy receiving maximal renin-angiotensin system blocker therapy, finerenone reduced the risk of cardiovascular death, non-fatal MI, non-fatal stroke or hospitalization due to HF compared with placebo [111]. In a pooled analysis of FIDELITY, the improvement in cardiovascular and renal outcomes in patients with type 2 DM and CKD under the effect of finerenone was confirmed [113]. Therefore, in people with type 2 DM and CKD with albuminuria who are receiving maximally tolerated doses of ACE inhibitors or ARBs, the addition of finerenone should be considered to improve cardiovascular outcomes and reduce the risk of CKD progression.

Features of the clinical use of drugs

In people with type 2 DM and a high risk of ACVD, HF, or CKD, therapy with SGLT-2 inhibitors and/or GLP-1 receptor agonists should be used as part of a comprehensive approach to reduce the risk of adverse cardiovascular and renal outcomes. Drugs of these classes should be included in therapy regimens regardless of the need for additional glycemic correction and the use of metformin. SGLT-2 inhibitors or agonists of GLP-1 receptors in combination with drugs for the treatment of AH, dyslipidemia, hyperglycemia, antiplatelet therapy will provide additional improvement of the of patients` prognosis. Therefore, their use should be initiated in people with diagnosed cardiovascular or renal disease who may subsequently be diagnosed with DM, as cardioprotective agents are appropriate to use from the start of DM treatment. The addition of SGLT-2 inhibitors or GLP-1 receptor agonists to therapy for long-term DM may be more challenging, especially if patients are already receiving complex glucose-lowering therapy. In such a case, treatment with SGLT-2 inhibitors or GLP-1 receptor agonists may require replacement of some or all of the previously prescribed glucose-lowering medications to minimize the risk of hypoglycemia and other adverse effects and to reduce treatment costs. Close collaboration between primary care physicians and specialists can help facilitate this adjustment of therapy and improve outcomes in people with type 2 DM who are at high risk for complications.

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