

Communication

Strategizing Cardiovascular Management in Diabetic Patients: Insights and Advancements from the 2023 ESC Guidelines for the Management of Cardiovascular Disease in Patients with Diabetes

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Abstract: Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality in individuals with type 2 diabetes mellitus (T2DM). The 2023 European Society of Cardiology (ESC) guidelines represent a significant advancement in the management of CVD in T2DM, building on the 2019 recommendations. Unlike previous iterations, the updated guidelines focus exclusively on T2DM, excluding pre-diabetes due to limited evidence directly linking it to cardiovascular risk. A notable addition is the SCORE2-Diabetes algorithm, which integrates diabetes-specific factors with traditional risk determinants to estimate the 10-year cardiovascular risk. This personalized risk stratification tool underscores the importance of early identification and management of key contributors, such as hyperglycemia and insulin resistance. The guidelines advocate for a multidisciplinary approach, emphasizing collaboration among diabetes, cardiovascular, and chronic kidney disease specialists to address the complex interplay of these conditions effectively. Moreover, the 2023 ESC guidelines highlight the necessity of individualized treatment strategies to reduce cardiovascular complications in T2DM. By reflecting the heterogeneity of diabetic populations and the evolving pharmacological landscape, these recommendations aim to optimize cardiovascular outcomes. This comprehensive update marks a critical step toward reducing the burden of CVD and improving the quality of life for patients with diabetes.

Keywords: Diabetes mellitus; SCORE2-Diabetes algorithm; Atherosclerotic cardiovascular disease; Heart failure

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with diabetes mellitus (DM). Individuals with diabetes are at a significantly increased risk for various forms of CVD, such as coronary artery disease (CAD), stroke, peripheral arterial disease, heart failure, and atrial fibrillation [1]. The complex interplay between hyperglycaemia, insulin resistance, and other risk factors promotes atherosclerosis and hypertension alongside other cardiovascular complications. The European Society of Cardiology (ESC) Congress 2023 offered an updated guideline on the management of cardiovascular disease in patients with diabetes [2].

Compared with the previous 2019 ESC Guidelines on diabetes which had included pre-diabetes and cardiovascular diseases, the 2023 updated guidelines did not include guidance in pre-diabetes due to the lack



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of a clear evidence-base [3]. In addition, the updated guidelines include a new focus on risk stratification and screening, diagnosis and treatment of cardiovascular disease in diabetes.

The guideline is designed for healthcare professionals specializing in diabetes, cardiovascular disease, and chronic kidney disease, providing a comprehensive framework to enhance patient care and outcomes. The detailed recommendation provides a roadmap for personalized and effective management strategies, reflecting the evolving landscape of diabetes care.

There are 5 main topics in the updated guidelines, each summarised below.

(1) Cardiovascular risk assessment in diabetes patients

Patients with type 2 DM (T2DM) are at very high risk of complications, increasing the medical burden and risk of adverse prognosis for these individuals. T2DM patients have a higher risk of cardiovascular morbidity and mortality. T2DM is associated with a 2- to 4-fold increase in the incidence of CAD and stroke, and a 2- to 8-fold greater heart failure risk [1]. Therefore, early detection and management are key to preventing the progression of these complications.

The updated guidelines highlighted the importance of cardiovascular risk assessment using the SCORE2-Diabetes algorithm, for patients aged ≥ 40 years in Europe with existing or new onset diabetes who do not have confirmed atherosclerotic cardiovascular disease (ASCVD) or severe target organ damage (TOD) [4]. This algorithm integrates both conventional CVD risk factors, such as age, smoking status, systolic blood pressure (SBP), total and high-density lipoprotein (HDL) -cholesterol, with diabetes-specific information including age at diabetes diagnosis, HbA1c, and eGFR (Figure 1). The aim is to determine the 10-year risk of fatal or non-fatal ASCVD (myocardial infarction or stroke) for each individual with diabetes. Once assessed with SCORE2-Diabetes, appropriate actions are undertaken to improve cardiovascular outcomes according to the patient’s risk stratification, categorized as low risk, intermediate risk, high risk, and very high risk.

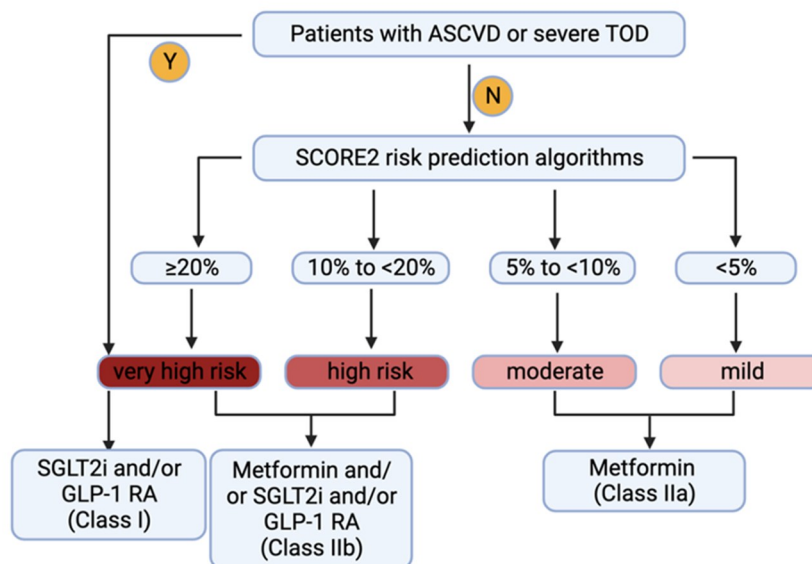


Figure 1. 10-year CVD risk using the SCORE2-Diabetes algorithm and glucose-lowering treatment. ASCVD, atherosclerotic cardiovascular disease; TOD, target-organ damage. Figure adapted from Marx et al. 2023 [2].

(2) Atherosclerotic cardiovascular disease risk reduction by glucose-lowering medication in diabetes

The meta-analysis of clinical trials in sodium-glucose cotransporter 2 inhibitors (SGLT2i) showed significant improvement in the reduction in the composite of time to the first event of CV death, MI, or stroke (MACE) in patients at high risk of or with established atherosclerotic cardiovascular disease [5]. In addition, such superior CV outcomes effects were also observed in the glucagon-like peptide-1 receptor agonists from later RCT trails (GLP-1RAs) [6]. Therefore, for patients with diabetes combined with ASCVD, the updated guidelines suggest that SGLT2i and/or GLP-1RAs are preferred, independent of glucose control

considerations, and independent of background metformin use. This therapeutic strategy aims to reduce the risk of cardiovascular and cerebrovascular events in addition to standard treatments such as antiplatelet agents, antihypertensive medications, and lipid-lowering drugs.

For diabetic patients without ASCVD or TOD, if their 10-year cardiovascular risk is equal to or exceeds 10%, it is recommended to start treatment with SGLT2i and/or GLP-1RA that offer cardiovascular outcomes benefits to diminish CVD risk.

(3) Management of heart failure with diabetes

The updated guidelines highlight the close relationship between diabetes and heart failure (HF) and offer a more comprehensive treatment approach. In T2DM patients, it is crucial to monitor heart failure symptoms and biomarkers, as well as echocardiographic functional and structural changes, to effectively manage the coexistence of these two diseases.

According to the recommendations, once the diabetic patients have been diagnosed with HF, regardless of the LVEF types (HFrEF, HFmrEF, and HFpEF), treatment with SGLT2 inhibitors, such as empagliflozin, dapagliflozin should be initiated to reduce the HF rehospitalization risk and CV death. GLP-1 RAs, sitagliptin/linagliptin, metformin, and insulin could be combined with SGLT2 inhibitors when needed for additional blood glucose lowering management, which have neutral effects on HF. Importantly, some glucose-lowering medications are associated with increased risk for HF rehospitalization. These include pioglitazone and saxagliptin which are therefore not recommended in DM patients with or at increased risk of HF.

(4) Enhance screening for atrial fibrillation in patients with diabetes

Patients with DM experience a 3% incremental risk for atrial fibrillation (AF) annually, which subsequently elevates the risk of stroke HF, and mortality. Recognizing that individuals with diabetes manifest an augmented risk of AF at relatively younger ages, the updated guidelines advocate for opportunistic screening of AF in those under 65 using either palpating pulse or ECG evaluations, particularly when concomitant risk factors are identifiable.

(5) Expanding treatment strategies for diabetes complicating chronic kidney disease

According to the updated guidelines, for patients with DM coexisting with chronic kidney disease (CKD), if their estimated glomerular filtration rate (eGFR) is >20 mL/min/1.73 m², the initiation of SGLT2 inhibitors (such as canagliflozin, empagliflozin, and dapagliflozin) are recommended to reduce the risks of cardiovascular disease (CVD) and CKD disease progression.

For patients with eGFR > 25 mL/min/1.73 m² who are already receiving treatment with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), the addition of the non-steroidal mineralocorticoid receptor antagonist (MRA) finerenone. Appropriate potassium monitoring is recommended although the likelihood of hyperkalemia appears to be lower when using finerenone compared to spironolactone. This therapeutic strategy aims to further diminish the risks of CVD and renal failure beyond the standard CKD treatments. In the FIGARO-DKD cardiovascular outcome trial, finerenone demonstrated a reduction in heart failure hospitalisation despite people with existing HFrEF being excluded for already having an indication for MRA treatment.

For patients with eGFR > 15 mL/min/1.73 m², treatment with GLP-1RAs is recommended.

For lipid-lowering treatment in DM patients with CKD, the initial therapy should combine statin drugs with ezetimibe. In CKD patients with associated ASCVD, the consideration of low-dose aspirin can be made. A combined treatment of ACEI and ARB is not recommended due to worse CV outcomes.

1. Takeaway Messages

Patients with DM have a higher risk of cardiovascular disease. Selecting medications for patients with DM should focus on reducing the risk of CVD and established CVD. Within the last decade, many RCTs have proven GLP-1 ARs and SGLT2i have CV benefits and have been approved for the treatment of diabetes and for the prevention of CV events [6,7]. Personalized treatment, which employs a shared decision-making strategy between patients and healthcare professionals, is increasingly adopted in the management of DM patients. Here we summarized ten takeaway messages from the ESC guidelines for the management of cardiovascular disease in patients with diabetes:

(1) Lifestyle interventions for reducing cardiovascular risk

The updated guidelines recommended modified lifestyles such as a Mediterranean diet, regular exercises smoking cessation, and weight control to decrease the risk of CVD in T2DM patients. By embracing these changes, individuals with T2DM can significantly reduce the risk of CVD, improving overall quality of life and outcomes. These lifestyle modifications are crucial components of a holistic approach to manage and prevent the progression of cardiovascular complications in T2DM.

(2) Updated treatment prioritization

Previous guidelines recommended that antihyperglycemic agents with proven CV benefits should be initiated after metformin in patients with increased risk of or established CVD, regardless of their glycosylated hemoglobin level. The updated guidelines recommend that metformin should be prescribed after GLP-1RAs and SGLT2 inhibitor when the patients need extra-glucose control in high risk of CVD and established CVD in T2DM patients (Figure 2). Therefore, GLP-1RAs and SGLT2 inhibitors become the frontline medication of T2DM with high-risk or established CVD patients.

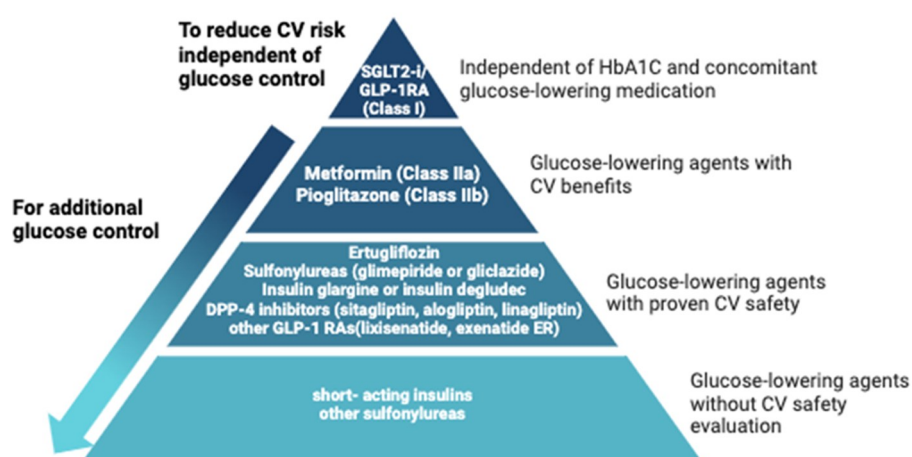


Figure 2. Glucose-lowering agents to reduce cardiovascular risk in patients with T2DM and ASCVD.

(3) Shift in heart failure management

Heart failure is a major cardiovascular complication of diabetes. The SGLT2 inhibitors, dapagliflozin and empagliflozin should be prescribed in patients with T2DM and LVEF > 40% (HFmrEF and HFpEF) as well as in HFrEF to reduce the risk of HF hospitalization or CV death according to the updated ESC guidelines (I, A). This recommendation has altered the landscape of HFpEF patient care, addressing the historical challenge of limited effective therapies to reduce mortality in recent decades. Based on clinical evidence from the STEP-HFpEF trial, HFpEF is recognized as a heterogeneous disease with diverse pathophysiologic drivers. It is recommended that patients with HFpEF, obesity, and diabetes be treated with both SGLT2 inhibitors and GLP-1RAs simultaneously [8].

(4) Comprehensive approach to diabetic kidney disease

In the treatment of patients with T2DM and CKD, the updated guidelines recommend statin-based regimen to reduce cardiovascular risk and initiating SGLT2 inhibitors alongside a maximum ACE-I or ARB, blood pressure control, and the non-steroidal MRA finerenone to reduce the risk of kidney failure and of the composite CV outcomes of CV death, non-fatal MI, non-fatal stroke, or hospitalization for HF in patients with CKD. In patients with T2DM and CKD, it is recommended to control blood pressure by targeting an SBP of ≤ 130 mmHg (but not < 120 mmHg) and a DBP of ≤ 80 mmHg (but not < 70 mmHg). This can be achieved using combinations of RAS inhibitors along with a calcium channel blocker or diuretic. For additional glucose-lowering medication cardiovascular benefits, GLP-1 RA is recommended. Therefore, statins, BP control, maximum ACE-I or ARB, SGLT2 inhibitor, and Finerenone were the five important intervention approaches for patients with T2DM and CKD (Figure 3).

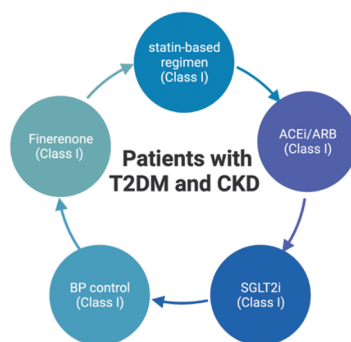


Figure 3. Pharmacotherapy mitigate cardiovascular and renal risks in T2DM patients with CKD. ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; BP, blood pressure; CKD, chronic kidney disease; T2DM, type 2 diabetes mellitus; SGLT2i, Sodium/glucose cotransporter-2 inhibitors.

(5) Antiplatelet strategies in different clinical contexts

The application of antiplatelet drugs varies in different clinical backgrounds of T2DM with acute coronary syndrome (ACS) and chronic coronary syndrome (CCS). For patients with diabetes and ACS, dual antiplatelet therapy (DAPT), specifically low-dose aspirin (ASA) combined with either prasugrel or ticagrelor, is preferred over DAPT with clopidogrel, and it is recommended for 12 months unless there is a very high risk of bleeding. For those with CCS who have undergone Percutaneous Coronary Intervention (PCI), DAPT involving clopidogrel and low-dose ASA is recommended for 6 months post-PCI. However, in the case of patients who have undergone coronary artery bypass grafting (CABG), a single antiplatelet therapy with low-dose ASA is recommended. When antithrombotic drugs are used in combination with antiplatelet drugs, proton pump inhibitors are recommended to prevent gastrointestinal bleeding.

(6) Multidisciplinary behavioral strategies

The updated ESC guidelines highlighted the importance of interdisciplinary cooperation and multifactorial approach to risk-factor management in DM patients. A predominant number of patients with T2DM do not achieve BP targets of $\leq 130/80$ mmHg and LDL-C levels of < 2.6 mmol/L in moderate-risk patients, LDL-C levels of < 1.8 mmol/L in high-risk patients, LDL-C levels < 1.4 mmol/L in very high-risk patients, due to the low prescription rates of comprehensive cardioprotective medications such as antiplatelet agents, beta-blockers, RAS inhibitors, and statins. Against this background, multidisciplinary behavioral strategies should be developed and implemented. These strategies should integrate the expertise and proficiency of various healthcare providers to enhance the overall care and management of T2DM patients.

(7) Early detection of lower extremity arterial disease

Lower extremity arterial disease (LEAD) is a prevalent complication among diabetes patients with poor outcomes. This type of diabetes present with an increased risk of chronic limb-threatening ischemia (CLTI) as the initial clinical manifestation of LEAD, emphasizing the importance of regular ankle-brachial index (ABI) measurements for early detection and diagnosis. The approach to managing LEAD remains uniform for patients with or without diabetes, with treatment strategies being primarily similar. However, revascularization options may be limited for diabetic patients due to the presence of diffuse and distal lesions.

(8) Tailored approaches for type 1 diabetes (T1DM)

In patients with T1DM, hyperglycemia stands out as the principal modifiable factor leading to complications later in life, implying that intensive diabetes therapy is pivotal in mitigating CV complications in T1DM. Implementing strategies such as regular exercise, a healthy lifestyle, lipid management, BP control, and antiplatelet therapies can mitigate the risk of CVD. Besides insulin, there have been concerns regarding the use of other glucose-lowering agents like GLP-1 RAs or SGLT2 inhibitors due to increased cases of symptomatic hypoglycemia, hyperglycemia, or euglycemic ketoacidosis. As a result, these agents are currently not indicated for T1DM.

(9) Person-centered care in diabetes management

The updated ESC guidelines highlighted the importance of person-centered care approach in managing diabetes, emphasizing shared decision-making and a comprehensive understanding of the patient's needs,

background, and culture when formulating health decisions and practices. This approach, executed through both direct interactions and telemedicine, fosters effective communication, education, and support, enhancing patients problem-solving skills, self-efficacy, self-care, motivation, and self-management. Incorporating such a tailored approach is crucial for successful self-management of diabetes and its comorbidities, encompassing education, motivation, empowerment, and continuous supportive care, resulting in increased patient satisfaction, higher adherence to therapeutic plans, and improved health outcomes.

(10) Atrial fibrillation screening in diabetic patients

The new guidelines also highlighted the importance of AF screening in diabetic patients due to the high prevalence. For DM patients aged ≥ 65 years, the screening could be pulse palpation or the use of wearable devices, with systematic ECG screening recommended when the age is ≥ 75 years to confirm AF presence. Furthermore, for aged < 65 years, opportunistic screening through pulse taking or ECG is recommended given the associated risk of AF and the potential consequent risk of ischemic stroke.

In conclusion, the updated guidelines are a comprehensive amalgamation of insights from specialists in diabetes, CVD, and CKD, offering a confluence of refined knowledge and pioneering advancements made in the field of diabetes treatment over the last decade. The guidelines accentuate the existence of unresolved queries and evidence gaps in the current knowledge, highlighting the need for continuous, evidence-based clinical studies to elucidate these ambiguous aspects and enhance patient care in diabetes. The guidelines have been the focus of extensive attention within the medical fraternity, illuminating the latest insights and treatment paradigms concerning the interconnectedness of diabetes, CVD, and CKD. It improves the integration of these newfound understandings into clinical practice, empowering physicians to elevate the standard of medical care provided to their patients. This representation of collective scholarly endeavour not only signifies a collaborative stride in the domains of diabetes, CVD, and CKD but also catalyzes transformative advancements in medical practice and the betterment of patient health.

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