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ESC GUIDELINES

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

Developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC)

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See the *European Heart Journal* online for supplementary documents that include background information and evidence tables.

Keywords Guidelines • Aortic and peripheral arterial diseases • Arrhythmias • Atrial fibrillation • Cardiovascular disease • Cardiovascular risk assessment • Chronic kidney disease • Coronary artery disease • Diabetes mellitus • Heart failure • Patient-centred care • Pharmacological treatment • Prevention • Risk factors

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Abbreviations and acronyms

2hPG	2 h plasma glucose
ABI	Ankle–brachial index
ABPM	Ambulatory blood pressure monitoring
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE-I	Angiotensin-converting enzyme inhibitor
ACS	Acute coronary syndrome
ADA	American Diabetes Association
ADAPTABLE	Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term
ADDITION	Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care
ADJUNCT ONE	The Efficacy and Safety of Liraglutide as Adjunct Therapy to Insulin in the Treatment of Type 1 Diabetes
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation
AF	Atrial fibrillation
ARB	Angiotensin-II receptor blocker
ARNI	Angiotensin receptor–neprilysin inhibitor
ARR	Absolute risk reduction
ASA	Acetylsalicylic acid
ASCEND	A Study of Cardiovascular Events iN Diabetes
ASCVD	Atherosclerotic cardiovascular disease
ATTACK	Aspirin to Target Arterial Events in Chronic Kidney Disease
b.i.d.	Twice a day
b.p.m.	Beats per minute
BANTING	Evaluation of Evolocumab Efficacy in Diabetic Adults With Hypercholesterolemia/Mixed Dyslipidemia
BARC	Bleeding Academic Research Consortium
BARI 2D	Bypass Angioplasty Revascularization Investigation 2 Diabetes
BERSON	Safety and Efficacy of Evolocumab in Combination With Statin Therapy in Adults With Diabetes and Hyperlipidemia or Mixed Dyslipidemia
BMI	Body mass index
BNP	B-type natriuretic peptide
BP	Blood pressure
CABG	Coronary artery bypass graft
CAC	Coronary artery calcium
CAD	Coronary artery disease
CANVAS	Canagliflozin Cardiovascular Assessment Study
CARMELINA	Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus
CAROLINA	Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes
CCB	Calcium channel blocker
CCS	Chronic coronary syndrome
CGM	Continuous glucose monitoring

CHA_2DS_2-VASc	Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes mellitus, Stroke or transient ischaemic attack (2 points), Vascular disease, Age 65–74 years, Sex category (female)
CHAP	Chronic Hypertension and Pregnancy
CHD	Coronary heart disease
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology/CKD Epidemiology Collaboration
CKD-MBD	Chronic kidney disease–mineral bone disorder
CLEAR	Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen
CLTI	Chronic limb-threatening ischaemia
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies
CPG	Clinical Practice Guidelines
CREDENCE	Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation
CRT	Cardiac resynchronization therapy
CRT-D	Cardiac resynchronization therapy with an implantable defibrillator
CRT-P	Cardiac resynchronization therapy-pacemaker
CT	Computed tomography
CTA	Computed tomography angiography
CURRENT-OASIS	Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent EveNTs/Optimal Antiplatelet Strategy for InterventionS
CV	Cardiovascular
CVD	Cardiovascular disease
CVOT	Cardiovascular outcomes trial
DAPA-CKD	Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease
DAPA-HF	Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure
DAPT	Dual antiplatelet therapy
DAT	Dual antithrombotic therapy
DBP	Diastolic blood pressure
DCCT	Diabetes Control and Complications Trial
DD	Double diabetes
DECLARE-TIMI 58	Dapagliflozin Effect on Cardiovascular Events –Thrombolysis In Myocardial Infarction 58
DELIVER	Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure
DES	Drug-eluting stent
DEVOTE	A Trial Comparing Cardiovascular Safety of Insulin Degludec vs Insulin Glargine in Patients With Type 2 Diabetes at High Risk of Cardiovascular Events
DIAL	Diabetes lifetime-perspective prediction
DIGAMI	Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction
DiRECT	Diabetes Remission Clinical Trial
DPP-4	Dipeptidyl peptidase-4
EACTS	European Association for Cardio-Thoracic Surgery
EASD	European Association for the Study of Diabetes
ECG	Electrocardiogram
EDC	Pittsburgh Epidemiology of Diabetes Complications
EDIC	Epidemiology of Diabetes Interventions and Complications
eGFR	Estimated glomerular filtration rate
ELIXA	Evaluation of Lixisenatide in Acute Coronary Syndrome
EMMY	Impact of EMpagliflozin on cardiac function and biomarkers of heart failure in patients with acute MYocardial infarction
EMPA-KIDNEY	The Study of Heart and Kidney Protection With Empagliflozin
EMPA-REG OUTCOME	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
EMPA-RESPONSE-AHF	Empagliflozin on Clinical Outcomes in Patients With Acute Decompensated Heart Failure
EMPEROR-Preserved	EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction
EMPEROR-Reduced	Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction
EMPULSE	A Study to Test the Effect of Empagliflozin in Patients Who Are in Hospital for Acute Heart Failure
EORP	EURObservational Research Programme
ER	Extended release
ESC	European Society of Cardiology
ESH	European Society of Hypertension
EXAMINE	Cardiovascular Outcomes Study of Alogliptin in Patients With Type 2 Diabetes and Acute Coronary Syndrome
EXSCEL	Exenatide Study of Cardiovascular Event Lowering
FIDELIO-DKD	Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease
FIGARO-DKD	Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease
FLOW	Effect of Semaglutide Versus Placebo on the Progression of Renal Impairment in Subjects With Type 2 Diabetes and Chronic Kidney Disease
FOURIER	Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk
FPG	Fasting plasma glucose
GDM	Gestational diabetes mellitus
GFR	Glomerular filtration rate
GLOBAL-LEADERS	A Clinical Study Comparing Two Forms of Antiplatelet Therapy After Stent Implantation
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
GRACE	Global Registry of Acute Coronary Events
HARMONY Outcomes	Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly

HbA1c	Glycated haemoglobin
HBPM	Home blood pressure monitoring
HCP	Healthcare professional
HDL-C	High-density lipoprotein-cholesterol
HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HMOD	Hypertension-mediated organ damage
HR	Hazard ratio
ICD	Implantable cardioverter defibrillator
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IHD	Ischaemic heart disease
IMPROVE-IT	Improved Reduction of Outcomes: Vytorin Efficacy International Trial
INR	International normalized ratio
IPD	Individual participant data
ISAR-REACT 5	Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment
ISCHEMIA	International Study of Comparative Health Effectiveness with Medical and Invasive Approaches
ISCHEMIA-CKD	International Study of Comparative Health Effectiveness with Medical and Invasive Approaches–Chronic Kidney Disease
ISTH	International Society of Thrombosis and Haemostasis
i.v.	Intravenous
J-DOIT3	Japan Diabetes Optimal Integrated Treatment Study for 3 Major Risk Factors of Cardiovascular Diseases
KDIGO	Kidney Disease: Improving Global Outcomes
KRT	Kidney replacement therapy
LDL-C	Low-density lipoprotein-cholesterol
LEAD	Lower-extremity artery disease
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
LIBERATES	Improving Glucose Control in Patients with Diabetes Following Myocardial Infarction: The Role of a Novel Glycaemia Monitoring Strategy
Look AHEAD	Action for Health in Diabetes
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
MRA	Mineralocorticoid receptor antagonist
NNH	Number needed to harm
NNT	Number needed to treat
NO	Nitric oxide
NOAC	Non-Vitamin K Antagonist Oral Anticoagulant
NSTE-ACS	Non-ST-elevation acute coronary syndrome
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
o.d.	Once a day
OAC	Oral anticoagulant
OARS	Open-ended questions, Affirmation, Reflective listening, and Summarizing
ODYSSEY DM-DYSLIPIDEMIA	Efficacy and Safety of Alirocumab Versus Usual Care on Top of Maximally Tolerated Statin Therapy in Patients With Type 2 Diabetes and Mixed Dyslipidemia
ODYSSEY OUTCOMES	Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab
OGTT	Oral glucose tolerance test
OMT	Optimal medical therapy
OR	Odds ratio
ORIGIN	Outcome Reduction With Initial Glargine Intervention
ORION	Inclisiran for Participants With Atherosclerotic Cardiovascular Disease and Elevated Low-density Lipoprotein Cholesterol
PA	Physical activity
PAD	Peripheral arterial diseases
PARAGON-HF	Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
PEGASUS-TIMI 54	Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin
PIONEER 6	Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes
PROactive	PROspective pioglitAzone Clinical Trial In macroVascular Events
QI	Quality indicator
QTc	Correct QT interval
RAS	Renin–angiotensin system
RCT	Randomized controlled trial
REDUCE-IT	Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention
REWIND	Researching Cardiovascular Events With a Weekly Incretin in Diabetes
ROS	Reactive oxygen species
RPG	Random plasma glucose
RR	Relative risk
SAPT	Single antiplatelet therapy
SAVOR-TIMI 53	Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus –Thrombolysis In Myocardial Infarction 53
SBP	Systolic blood pressure
s.c.	Subcutaneous
SCD	Sudden cardiac death
SCORED	Effect of Sotagliflozin on Cardiovascular and Renal Events in Participants With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk
SCORE2-Diabetes	type 2 diabetes-specific 10-year CVD risk score
SCORE2-OP	SCORE2-older persons
SGLT2	Sodium–glucose co-transporter-2
SMART	Specific, Measurable, Achievable, Realistic, Timely

SOLOIST-WHF	Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure
STEMI	ST-elevation myocardial infarction
STRONG-HF	Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP testinG, of Heart Failure Therapies
SUSTAIN 6	Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TAT	Triple antithrombotic therapy
TBI	Toe–brachial index
$TcPO_2$	Transcutaneous oxygen pressure
TECOS	Trial Evaluating Cardiovascular Outcomes with Sitagliptin
TG	Triglyceride
THEMIS	Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study
TIMI	Thrombolysis in Myocardial Infarction
TOD	Target-organ damage
TRACK	Treatment of CVD with Low Dose Rivaroxaban in Advanced CKD
TRL	Triglyceride-rich lipoprotein
TROPICAL-ACS	Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes
TSAT	Transferrin saturation
TZD	Thiazolidinedione
UACR	Urine albumin-to-creatinine ratio
UKPDS	United Kingdom Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial
VALUE	Valsartan Antihypertensive Long-term Use Evaluation
VERTIS CV	Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial
VKA	Vitamin K antagonist
WHO	World Health Organization
WIfI	Wound, Ischaemia, foot Infection

1. Preamble

Guidelines evaluate and summarize available evidence, with the aim of assisting health professionals in proposing the best diagnostic or therapeutic approach for an individual patient with a given condition. Guidelines are intended for use by health professionals and the European Society of Cardiology (ESC) makes its Guidelines freely available.

ESC Guidelines do not override the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient or the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and regulations applicable in each country to drugs and devices at the time of prescription, and, where appropriate, to respect the ethical rules of their profession.

ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated. ESC Policies and Procedures for formulating and issuing ESC Guidelines can be found on the ESC website (https://www.escardio.org/Guidelines).

The Members of this Task Force were selected by the ESC to represent professionals involved with the medical care of patients with this pathology. The selection procedure aimed to include members from across the whole of the ESC region and from relevant ESC Subspecialty Communities. Consideration was given to diversity and inclusion, notably with respect to gender and country of origin. The Task Force performed a critical evaluation of diagnostic and therapeutic approaches, including assessment of the risk-benefit ratio. The strength of every recommendation and the level of evidence supporting them were weighed and scored according to pre-defined scales as outlined below. The Task Force followed ESC voting procedures, and all approved recommendations were subject to a vote and achieved at least 75% agreement among voting members.

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. Their declarations of interest were reviewed according to the ESC declaration of interest rules and can be found on the ESC website (http://www.escardio.org/Guidelines), and have been compiled in a report published in a supplementary document with the guidelines. The Task Force received its entire financial support from the ESC without any involvement from the healthcare industry.

The ESC Clinical Practice Guidelines (CPG) Committee supervises and co-ordinates the preparation of new guidelines and is responsible for the approval process. ESC Guidelines undergo extensive review by the CPG Committee and external experts, including members from across the whole of the ESC region and from relevant ESC Subspecialty Communities and National Cardiac Societies. After appropriate revisions, the guidelines are signed off by all the experts involved in the Task Force. The finalized document is signed off by the CPG Committee for publication in the *European Heart Journal*. The guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their writing. Tables of evidence summarizing the findings of studies informing development of the guidelines are included. The ESC warns readers that the technical language may be misinterpreted and declines any responsibility in this respect.

Off-label use of medication may be presented in the current Guidelines if a sufficient level of evidence shows that it can be considered medically appropriate for a given condition. However, the final decisions concerning an individual patient must be made by the responsible health professional giving special consideration to:

- The specific situation of the patient. Unless otherwise provided for by national regulations, off-label use of medication should be limited to situations where it is in the patient's interest with regard to the quality, safety, and efficacy of care, and only after the patient has been informed and has provided consent.
- Country-specific health regulations, indications by governmental drug regulatory agencies, and the ethical rules to which health professionals are subject, where applicable.

2. Introduction

Patients with diabetes are at increased risk of developing cardiovascular disease (CVD) with its manifestations of coronary artery disease (CAD), heart failure (HF), atrial fibrillation (AF), and stroke, as well as aortic and peripheral artery diseases. In addition, diabetes is a major risk factor for developing chronic kidney disease (CKD), which in itself is associated

Table 1 **Classes of recommendations**

Classes of recommendations	Definition	Wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Table 2 **Levels of evidence**

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

with developing CVD. The combination of diabetes with these cardio-renal comorbidities enhances the risk not only for cardiovascular (CV) events but also for CV and all-cause mortality. The current European Society of Cardiology (ESC) Guidelines on the management of cardiovascular disease in patients with diabetes are designed to guide prevention and management of the manifestations of CVD in patients with diabetes based on data published until end of January 2023. Over the last decade, the results of various large cardiovascular outcome trials (CVOTs) in patients with diabetes at high CV risk with novel glucose-lowering agents, such as sodium–glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists (RAs), but also novel non-steroidal mineralocorticoid receptor antagonists (MRAs), such as finerenone have substantially expanded available therapeutic options, leading to numerous evidence-based recommendations for the management of this patient population.

The current Guidelines—in contrast to the previous 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases—only focus on CVD and diabetes and, given the lack of clear evidence, leave aside the aspect of pre-diabetes. In addition, this version of the Guidelines gives recommendations on stratifying CV risk, as well as on screening, diagnosis, and treatment of CVD in patients with diabetes. For all other aspects concerning the management of patients with diabetes, we refer to the recommendations from diabetes associations, e.g. the European Association for the Study of Diabetes (EASD) or the American Diabetes Association (ADA).[1]

These Guidelines offer evidence-based recommendations to manage CV risk in patients with diabetes and provide guidance for the treatment of atherosclerotic cardiovascular disease (ASCVD) in patients with diabetes. To individualize treatment strategies, the current Guidelines introduce a novel, dedicated, type 2 diabetes mellitus (T2DM)-specific,

10-year CVD risk score (SCORE2-Diabetes) for patients with T2DM without ASCVD or severe target-organ damage (TOD). This score, which now extends the established SCORE2 prediction algorithm for T2DM, provides data on the 10-year risk of fatal and non-fatal CVD events (myocardial infarction [MI], stroke) based on individual patient characteristics. SCORE2-Diabetes serves as a guide for clinical decision-making in patients with T2DM at low, moderate, high, or very high risk, but without clinically overt ASCVD or severe TOD.

Given the high prevalence of undetected diabetes in patients with CVD, as well as the elevated risk and therapeutic consequences if both co-morbidities co-exist, these Guidelines recommend systematic screening for diabetes in all patients with CVD. In addition, all patients with diabetes need to be evaluated for risk and presence of CVD and CKD. Based on evidence from large CVOTs, the current Guidelines provide clear recommendations on how to treat patients with diabetes and clinical manifestations of cardiovascular-renal disease. As such, in patients with diabetes and ASCVD, treatment with GLP-1 RAs and/or SGLT2 inhibitors is recommended to reduce CV risk, independent of glucose control and in addition to standard of care, e.g. antiplatelet, anti-hypertensive, or lipid-lowering therapy. A special focus of these Guidelines is on managing HF in diabetes, a field that has been underestimated for years. Based on data from large CVOTs, it is recommended to treat patients with diabetes and chronic HF (independent of left ventricular ejection fraction [LVEF]) with SGLT2 inhibitors to reduce HF hospitalization. Finally, in patients with diabetes and CKD, it is recommended to treat with an SGLT2 inhibitor and/or finerenone, since these agents reduce CV and kidney failure risk on top of standard of care (*Figure 1*).

Managing patients with diabetes and CVD requires an interdisciplinary approach, which should involve healthcare clinicians from different disciplines and areas of expertise to support shared decision-making and implement a personalized treatment strategy to reduce each patient's disease burden. Ultimately, our common goal in managing CVD in patients with diabetes is to improve patients' prognosis and health-related quality of life.

2.1. Central figure

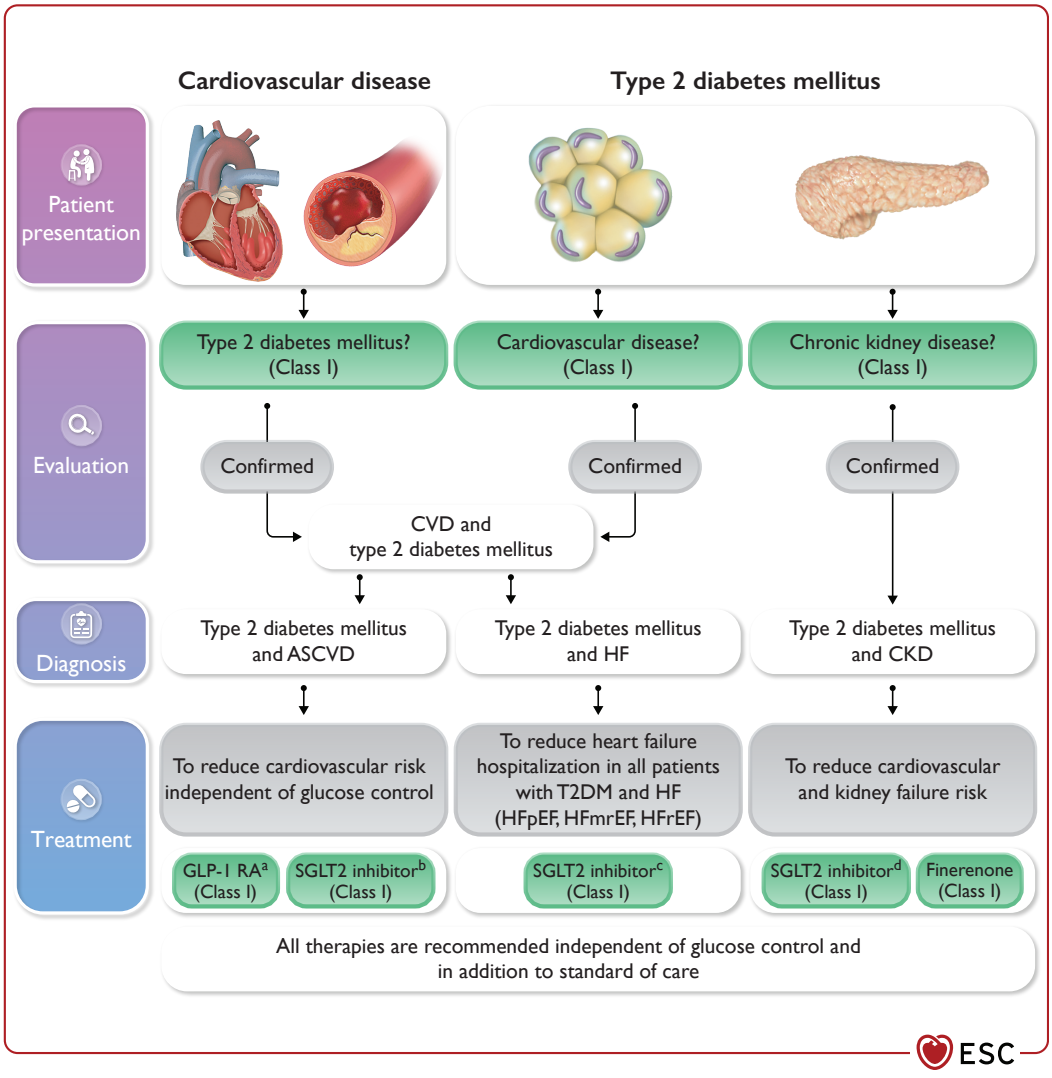

Figure 1 Management of cardiovascular disease in patients with type 2 diabetes: clinical approach and key recommendations. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; s.c. subcutaneous; SGLT2, sodium–glucose co-transporter-2; T2DM, type 2 diabetes mellitus. [a]GLP-1 RAs with proven cardiovascular benefit: lir-aglutide, semaglutide s.c., dulaglutide, efpeglenatide. [b]SGLT2 inhibitors with proven cardiovascular benefit: empagliflozin, canagliflozin, dapagliflozin, sotagli-flozin. [c]Empagliflozin, dapagliflozin, sotagliflozin in HFrEF; empagliflozin, dapagliflozin in HFpEF and HFmrEF. [d]Canagliflozin, empagliflozin, dapagliflozin.

2.2. What is new

Table 3 New recommendations

Recommendations	Class[a]	Level[b]
Cardiovascular risk assessment in diabetes—*Section 4*		
In patients with T2DM without symptomatic ASCVD or severe TOD, it is recommended to estimate 10-year CVD risk via SCORE2-Diabetes.	I	B
Weight reduction in patients with diabetes—*Section 5.1.1*		
It is recommended that individuals living with overweight or obesity aim to reduce weight and increase physical exercise to improve metabolic control and overall CVD risk profile.	I	A
Glucose-lowering medications with effects on weight loss (e.g. GLP-1 RAs) should be considered in patients with overweight or obesity to reduce weight.	IIa	B
Bariatric surgery should be considered for high and very high risk patients with BMI ≥35 kg/m^2 (≥Class II) when repetitive and structured efforts of lifestyle changes combined with weight-reducing medications do not result in maintained weight loss.	IIa	B
Increasing physical activity and exercise in patients with diabetes—*Section 5.1.3*		
It is recommended to adapt exercise interventions to T2DM-associated comorbidities, e.g. frailty, neuropathy, or retinopathy.	I	B
It is recommended to introduce structured exercise training in patients with T2DM and established CVD, e.g. CAD, HFpEF, HFmrEF, HFrEF, or AF to improve metabolic control, exercise capacity, and quality of life, and to reduce CV events.	I	B
The use of behavioural theory-based interventions, such as goal-setting, re-evaluation of goals, self-monitoring, and feedback, should be considered to promote physical activity behaviour.	IIa	B
It may be considered to use wearable activity trackers to increase physical activity behaviour.	IIb	B
Smoking cessation in patients with diabetes—*Section 5.1.4*		
Nicotine replacement therapy, varenicline, and bupropion, as well as individual or telephone counselling, should be considered to improve smoking cessation success rate.	IIa	B
Glycaemic targets—*Section 5.2*		
Tight glycaemic control should be considered for reducing CAD in the long term, preferably using agents with proven CV benefit.	IIa	B
Atherosclerotic cardiovascular disease risk reduction by glucose-lowering medications in diabetes—*Section 5.3*		
It is recommended to prioritize the use of glucose-lowering agents with proven CV benefits followed by agents with proven CV safety over agents without proven CV benefit or proven CV safety.	I	C
If additional glucose control is needed, metformin should be considered in patients with T2DM and ASCVD.	IIa	C
If additional glucose control is needed, pioglitazone may be considered in patients with T2DM and ASCVD without HF.	IIb	B
Blood pressure and diabetes—*Section 5.4*		
Regular BP measurements are recommended in all patients with diabetes to detect and treat hypertension to reduce CV risk.	I	A
Lipids and diabetes—*Section 5.5*		
A PCSK9 inhibitor is recommended in patients at very high CV risk, with persistently high LDL-C levels above target despite treatment with a maximum tolerated statin dose, in combination with ezetimibe, or in patients with statin intolerance.	I	A
If a statin-based regimen is not tolerated at any dosage (even after re-challenge), a PCSK9 inhibitor added to ezetimibe should be considered.	IIa	B
If a statin-based regimen is not tolerated at any dosage (even after re-challenge), ezetimibe should be considered.	IIa	C
High-dose icosapent ethyl (2 g b.i.d.) may be considered in combination with a statin in patients with hypertriglyceridaemia.	IIb	B
Antithrombotic therapy in patients with diabetes—*Section 5.6*		
Clopidogrel 75 mg o.d. following appropriate loading (e.g. 600 mg or at least 5 days already on maintenance therapy) is recommended in addition to ASA for 6 months following coronary stenting in patients with CCS, irrespective of stent type, unless a shorter duration is indicated due to the risk or occurrence of life-threatening bleeding.	I	A
In patients with diabetes and ACS treated with DAPT who are undergoing CABG and do not require long-term OAC therapy, resuming a $P2Y_{12}$ receptor inhibitor as soon as deemed safe after surgery and continuing it up to 12 months is recommended.	I	C
Adding very low-dose rivaroxaban to low-dose ASA for long-term prevention of serious vascular events should be considered in patients with diabetes and CCS or symptomatic PAD without high bleeding risk.	IIa	B

Continued

In patients with ACS or CCS and diabetes undergoing coronary stent implantation and having an indication for anticoagulation prolonging triple therapy with low-dose ASA, clopidogrel, and an OAC should be considered up to 1 month if the thrombotic risk outweighs the bleeding risk in the individual patient.	IIa	C
In patients with ACS or CCS and diabetes undergoing coronary stent implantation and having an indication for anticoagulation prolonging triple therapy with low-dose ASA, clopidogrel, and an OAC up to 3 months may be considered if the thrombotic risk outweighs the bleeding risk in the individual patient.	IIb	C
When clopidogrel is used, omeprazole and esomeprazole are not recommended for gastric protection.	III	B
Multifactorial approach in patients with diabetes—*Section 5.7*		
Identifying and treating risk factors and comorbidities early is recommended.	I	A
Multidisciplinary behavioural approaches that combine the knowledge and skills of different caregivers are recommended.	I	C
Principles of motivational interviewing should be considered to induce behavioural changes.	IIa	C
Telehealth may be considered to improve risk profile.	IIb	B
Management of coronary artery disease in patients with diabetes—*Section 6*		
Myocardial revascularization in CCS is recommended when angina persists despite treatment with anti-anginal drugs or in patients with a documented large area of ischaemia (>10% LV).	I	A
Complete revascularization is recommended in patients with STEMI without cardiogenic shock and with multivessel CAD.	I	A
It is recommended to assess glycaemic status at initial evaluation in all patients with ACS.	I	B
Complete revascularization should be considered in patients with NSTE-ACS without cardiogenic shock and with multivessel CAD.	IIa	C
Glucose-lowering therapy should be considered in patients with ACS with persistent hyperglycaemia, while episodes of hypoglycaemia should be avoided.	IIa	C
Routine immediate revascularization of non-culprit lesions in patients with MI and multivessel disease presenting with cardiogenic shock is not recommended.	III	B

Continued

Heart failure and diabetes—*Section 7*		
Evaluation for heart failure in diabetes		
If HF is suspected, it is recommended to measure BNP/NT-proBNP.	I	B
Systematic survey for HF symptoms and/or signs of HF is recommended at each clinical encounter in all patients with diabetes.	I	C
Diagnostic tests in all patients with suspected heart failure		
12-lead ECG is recommended.	I	C
Transthoracic echocardiography is recommended.	I	C
Chest radiography (X-ray) is recommended.	I	C
Routine blood tests for comorbidities are recommended, including full blood count, urea, creatinine and electrolytes, thyroid function, lipids, and iron status (ferritin and TSAT).	I	C
Pharmacological treatment indicated in patients with HFrEF (NYHA class II–IV) and diabetes		
SGLT2 inhibitors (dapagliflozin, empagliflozin, or sotagliflozin) are recommended in all patients with HFrEF and T2DM to reduce the risk of HF hospitalization and CV death.	I	A
An intensive strategy of early initiation of evidence-based treatment (SGLT2 inhibitors, ARNI/ACE-Is, beta-blockers, and MRAs), with rapid up-titration to trial-defined target doses starting before discharge and with frequent follow-up visits in the first 6 weeks following a HF hospitalization is recommended to reduce re-admissions or mortality.	I	B
Other treatments indicated in selected patients with HFrEF (NYHA class II–IV) and diabetes		
Hydralazine and isosorbide dinitrate should be considered in self-identified Black patients with diabetes and LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA class III–IV despite treatment with an ACE-I (or ARNI), a beta-blocker, and an MRA, to reduce the risk of HF hospitalization and death.	IIa	B
Digoxin may be considered in patients with symptomatic HFrEF in sinus rhythm despite treatment with sacubitril/valsartan or an ACE-I, a beta-blocker, and an MRA, to reduce the risk of hospitalization.	IIb	B
Heart failure treatments in patients with diabetes and LVEF >40%		
Empagliflozin or dapagliflozin are recommended in patients with T2DM and LVEF >40% (HFmrEF and HFpEF) to reduce the risk of HF hospitalization or CV death.	I	A

Continued

Special considerations for glucose-lowering medications in patients with T2DM with and without HF		
It is recommended to switch glucose-lowering treatment from agents without proven CV benefit or proven safety to agents with proven CV benefit.	I	C
Atrial fibrillation and diabetes—*Section 8.1*		
Opportunistic screening for AF by pulse taking or ECG is recommended in patients with diabetes <65 years of age (particularly when other risk factors are present) because patients with diabetes exhibit a higher AF frequency at a younger age.	I	C
Systematic ECG screening should be considered to detect AF in patients aged ≥75 years, or those at high risk of stroke.	IIa	B
Chronic kidney disease and diabetes—*Section 9*		
Intensive LDL-C lowering with statins or a statin/ezetimibe combination is recommended.	I	A
A SGLT2 inhibitor (canagliflozin, empagliflozin, or dapagliflozin) is recommended in patients with T2DM and CKD with an eGFR ≥20 mL/min/1.73 m^2 to reduce the risk of CVD and kidney failure.	I	A
Finerenone is recommended in addition to an ACE-I or ARB in patients with T2DM and eGFR >60 mL/min/1.73 m^2 with a UACR ≥30 mg/mmol (≥300 mg/g), or eGFR 25–60 mL/min/1.73 m^2 and UACR ≥3 mg/mmol (≥30 mg/g) to reduce CV events and kidney failure.	I	A
Low-dose ASA (75–100 mg o.d.) is recommended in patients with CKD and ASCVD.	I	A
Treatment with intensive medical or an initial invasive strategy is recommended in people with CKD, diabetes, and stable moderate or severe CAD, due to similar outcomes.	I	B
Kidney specialist advice may be considered for managing a raised serum phosphate, other evidence of CKD-MBD, and renal anaemia.	IIb	C
Combined use of an ARB with an ACE-I is not recommended.	III	B

Continued

Aortic and peripheral arterial diseases and diabetes—*Section 10*		
In patients with diabetes and aortic aneurysm, it is recommended to implement the same diagnostic work-up and therapeutic strategies (medical, surgical, or endovascular) as in patients without diabetes.	I	C
Type 1 diabetes and cardiovascular disease—*Section 11*		
In patients with T1DM, it is recommended that adjustment of glucose-lowering medication follows principles of patient self-management under the guidance of the diabetes healthcare multidisciplinary team.	I	C
Avoiding hypoglycaemic episodes is recommended, particularly in those with established CVD.	I	C
Statins should be considered for LDL-C lowering in adults older than 40 years with T1DM without a history of CVD to reduce CV risk.	IIa	B
Statins should be considered for use in adults younger than 40 years with T1DM and other risk factors of CVD or microvascular end-organ damage or 10-year CVD risk ≥10% to reduce CVD risk.	IIa	B
The use of the Scottish/Swedish risk prediction model may be considered to estimate 10-year CVD risk in patients with T1DM.	IIb	B

ACE-I, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AF, atrial fibrillation; ARB, angiotensin-II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; ASA, acetylsalicylic acid; ASCVD, atherosclerotic cardiovascular disease; b.i.d., twice a day; BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCS, chronic coronary syndrome; CKD-MBD, chronic kidney disease–mineral bone disorder; CV, cardiovascular; CVD, cardiovascular disease; DAPT, dual antiplatelet therapy; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LDL-C, low-density lipoprotein-cholesterol; LV, left ventricular/ventricle; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NSTE-ACS, non-ST-elevation acute coronary syndrome; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OAC, oral anticoagulant; o.d., once daily; PAD, peripheral arterial disease; PCSK9, proprotein convertase subtilisin/kexin type 9; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TOD, target-organ damage; TSAT, transferrin saturation; SCORE2-Diabetes, type 2 diabetes-specific 10-year CVD risk score; SGLT2, sodium–glucose co-transporter-2; STEMI, ST-elevation myocardial infarction; UACR, urinary albumin-to-creatinine ratio.

[a]Class of recommendation.

[b]Level of evidence.

Table 4 Revised recommendations

2019	Class[a]	Level[b]	2023	Class[a]	Level[b]
Change in diet and nutrition in patients with diabetes—*Section 5.1.2*					
A Mediterranean diet, rich in polyunsaturated and monounsaturated fats, should be considered to reduce CV events.	IIa	B	It is recommended to adopt a Mediterranean or plant-based diet with high unsaturated fat content to lower CV risk.	I	A
Atherosclerotic cardiovascular disease risk reduction by glucose-lowering medications in diabetes—*Section 5.3*					
Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk to reduce CV events.	I	A	SGLT2 inhibitors with proven CV benefit are recommended in patients with T2DM and ASCVD to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.	I	A
			In patients with T2DM without ASCVD or severe TOD but with a calculated 10-year CVD risk ≥10%, treatment with an SGLT2 inhibitor or GLP-1 RA may be considered to reduce CV risk.	IIb	C
Liraglutide, semaglutide, or dulaglutide are recommended in patients with T2DM and CVD, or at very high/high CV risk to reduce CV events.	I	A	GLP-1 RAs with proven CV benefit are recommended in patients with T2DM and ASCVD to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.	I	A
			In patients with T2DM without ASCVD or severe TOD but with a calculated 10-year CVD risk ≥10%, treatment with an SGLT2 inhibitor or GLP-1 RA may be considered to reduce CV risk.	IIb	C
Antithrombotic therapy in patients with diabetes—*Section 5.6*					
When low-dose aspirin is used, proton pump inhibitors should be considered to prevent gastrointestinal bleeding.	IIa	A	When antithrombotic drugs are used in combination, proton pump inhibitors are recommended to prevent gastrointestinal bleeding.	I	A
			When a single antiplatelet or anticoagulant drug is used, proton pump inhibitors should be considered to prevent gastrointestinal bleeding, considering the bleeding risk of the individual patient.	IIa	A
Multifactorial approach to risk-factor management in patients with diabetes—*Section 5.7*					
A multifactorial approach to diabetes management with treatment targets should be considered in patients with diabetes and CVD.	IIa	B	A multifactorial approach to managing T2DM with treatment targets is recommended.	I	B
Heart failure and diabetes—*Section 7*					
GLP-1 RAs (lixisenatide, liraglutide, semaglutide, exenatide, dulaglutide) have a neutral effect on the risk of HF hospitalization, and may be considered for diabetes treatment in patients with HF.	IIb	A	GLP-1 RAs (lixisenatide, liraglutide, semaglutide, exenatide ER, dulaglutide, efpeglenatide) have a neutral effect on the risk of HF hospitalization, and should be considered for glucose-lowering treatment in patients with T2DM at risk of or with HF.	IIa	A
Insulin may be considered in patients with advanced, systolic HFrEF.	IIb	C	Basal insulins (glargine and degludec) have a neutral effect on the risk of HF hospitalization, and should be considered for glucose-lowering treatment in patients with T2DM at risk of or with HF.	IIa	B
Atrial fibrillation and diabetes—*Section 8.1*					
Screening for AF by pulse palpation should be considered in patients aged >65 years with diabetes and confirmed by ECG, if any suspicion of AF, as AF in patients with diabetes increases morbidity and mortality.	IIa	C	Opportunistic screening for AF by pulse taking or ECG is recommended in patients ≥65 years of age.	I	B

Continued

Chronic kidney disease and diabetes—*Section 9*					
Treatment with the GLP-1 RAs liraglutide and semaglutide is associated with a lower risk of renal endpoints and should be considered for diabetes treatment if eGFR is >30 mL/min/1.73 m^2.	IIa	B	A GLP-1 RA is recommended at an eGFR >15 mL/min/1.73 m^2 to achieve adequate glycaemic control, due to low risk of hypoglycaemia and beneficial effects on weight, CV risk, and albuminuria.	I	A

AF, atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ER, extended release; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; SGLT2, sodium–glucose co-transporter-2; T2DM, type 2 diabetes mellitus; TOD, target-organ damage.
[a]Class of recommendation.
[b]Level of evidence.

Table 5 Revised concepts 2023 Guidelines

Focus of the Guidelines is prevention and management of cardiovascular disease in diabetes
The aspect of pre-diabetes is no longer covered in the current Guidelines.
Cardiovascular risk assessment in diabetes
For patients without ASCVD or severe target-organ damage, a novel T2DM-specific risk score (SCORE2-Diabetes) is introduced.
CV risk categories in T2DM are now defined based on the presence of ASCVD or severe target-organ damage or the 10-year CVD risk using SCORE2-Diabetes.
Atherosclerotic cardiovascular risk reduction by glucose-lowering medications in diabetes
Based on various meta-analyses including data from CVOTs with SGLT2 inhibitors and GLP-1 RAs, the current Guidelines give separate recommendations for patients with and without ASCVD/severe target-organ damage.
Special attention is given on the aspect of proven CV benefit and/or safety of glucose-lowering medications.
Heart failure and diabetes
Detailed recommendations are given on HF screening and diagnosis in patients with diabetes.
Based on data from outcome trials in patients with HF (HFrEF, HFmrEF, HFpEF) with and without diabetes, the current Guidelines provide recommendations for the treatment of HF in patients with diabetes across the whole spectrum of left ventricular ejection fraction.
Detailed recommendations are given for the use of glucose-lowering medications in patients with HF and diabetes.
Arrhythmias and diabetes
Given that patients with diabetes exhibit a higher AF frequency at a younger age, the concept of opportunistic screening for AF by pulse taking or ECG in patients with diabetes <65 years of age (particularly when other risk factors are associated) is introduced.
Chronic kidney disease and diabetes
A dedicated section on managing CV risk in patients with CKD and diabetes is introduced covering aspects of screening (including regular screening with eGFR and UACR) and treatment.

AF, atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; SCORE2-Diabetes, type 2 diabetes-specific 10-year CVD risk score; SGLT2, sodium–glucose co-transporter-2; T2DM, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio.

3. Diagnosis of diabetes

Diabetes mellitus, a common metabolic condition, affected 537 million individuals worldwide in 2021 (10.5% prevalence), and this is expected to rise to 783 million cases by 2045 (12.2% prevalence).[2]

Diabetes is suspected in the presence of specific symptoms, including polyuria, polydipsia, fatigue, blurred vision, weight loss, poor wound healing, and recurrent infections. However, the condition can be asymptomatic and is therefore undiagnosed in over 40% of adults worldwide (ranging from 24% to 75% across regions).[3] Abnormal glucose metabolism has been divided into two clinical categories: diabetes and pre-diabetes, which are biochemical definitions (discussed below).

3.1. Laboratory criteria for diagnosing diabetes and pre-diabetes

Several biochemical tests are used to diagnose diabetes, including fasting glucose, 2 h glucose (during the glucose tolerance test), random glucose, and glycated haemoglobin (HbA1c).[4–7]

3.1.1. Fasting glucose

Fasting glucose levels ≥7.0 mmol/L (≥126 mg/dL) is diagnostic of diabetes, although two tests are usually recommended to diagnose in the absence of hyperglycaemic symptoms. In patients with typical symptoms, a single test is adequate, and it should be noted that fasting is defined as no caloric intake for at least 8 h.

While international guidelines agree on the cut-off value for diagnosing diabetes, they are divided on the criteria for diagnosing pre-diabetes. The World Health Organization (WHO) defines pre-diabetes as fasting glucose levels 6.1–6.9 mmol/L (110–125 mg/dL) with levels <6.1 mmol/L (<110 mg/dL) regarded as normal.[5] However, the ADA has more stringent criteria, with glucose levels 5.6–6.9 mmol/L (100–125 mg/dL) falling into the pre-diabetes range and only those with glucose <5.6 mmol/L (<100 mg/dL) classified as having normal glucose metabolism.[7,8]

3.1.2. Two-hour oral glucose tolerance test and random glucose

Following an oral glucose load equivalent to 75 g glucose, 2 h glucose ≥11.1 mmol/L (≥200 mg/dL) is diagnostic of diabetes. Two-hour glucose 7.8–11.0 mmol/L (140–199 mg/dL) indicates impaired glucose tolerance, and the individual is diagnosed with pre-diabetes. However, an oral glucose tolerance test (OGTT) is not routinely performed, as it is time-consuming and inconvenient, and is therefore usually reserved for unclear cases. Of note, OGTT should be performed under resting conditions, as exercise during the test can invalidate the results.

Following on, a random glucose ≥11.1 mmol/L (≥200 mg/dL) is also diagnostic of diabetes in the presence of symptoms. In the absence of symptoms, two random glucose levels ≥11.1 mmol/L (≥200 mg/dL) are required to diagnose diabetes. One-hour OGTT ≥8.6 mmol/L (≥155 mg/dL) has been suggested as a better predictor of diabetes than 2 h OGTT ≥11.1 mmol/L (≥200 mg/dL), and is associated with vascular complications and mortality.[9] However, further validation is required before this new measure is widely adopted.

3.1.3. Glycated haemoglobin

Following high-quality epidemiological studies, it was suggested that HbA1c could be used to diagnose diabetes, and this was subsequently endorsed by international guidelines.[10] It should be noted that epidemiological studies have relied on the adult population, though HbA1c is also used in younger individuals as a diagnostic test.[11] Advantages of HbA1c include ease of measurement, limited within-individual variability, and the convenience of anytime testing without the need for fasting or a cumbersome OGTT.

However, HbA1c is not accurate in specific groups where the relationship between HbA1c and glucose levels is altered for any reason (Supplementary data online, *Table S1*).[12,13] Moreover, in cases of shorter diabetes duration, such as early type 1 diabetes mellitus (T1DM) or

Table 6 Biochemical diagnostic criteria for diabetes and pre-diabetes according to the World Health Organization and the American Diabetes Association

Glycaemic marker	WHO criteria (2011, 2019)[5,6]	ADA criteria (2021)[7]
	Diabetes	
FPG	≥7.0 mmol/L (≥126 mg/dL)	
2hPG (OGTT)	≥11.1 mmol/L (≥200 mg/dL)	
HbA1c	≥6.5% (≥48 mmol/mol)	
RPG	≥11.1 mmol/L (≥200 mg/dL)	
	Pre-diabetes	
FPG	6.1–6.9 mmol/L (110–125 mg/dL)	5.6–6.9 mmol/L (100–125 mg/dL)
2hPG (OGTT)	7.8–11.0 mmol/L (140–199 mg/dL)	
HbA1c	6.0–6.4% (42–47 mmol/mol)	5.7–6.4% (39–47 mmol/mol)

ADA, American Diabetes Association; 2hPG, 2 h plasma glucose; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; RPG, random plasma glucose; OGTT, oral glucose tolerance test; WHO, World Health Organization.

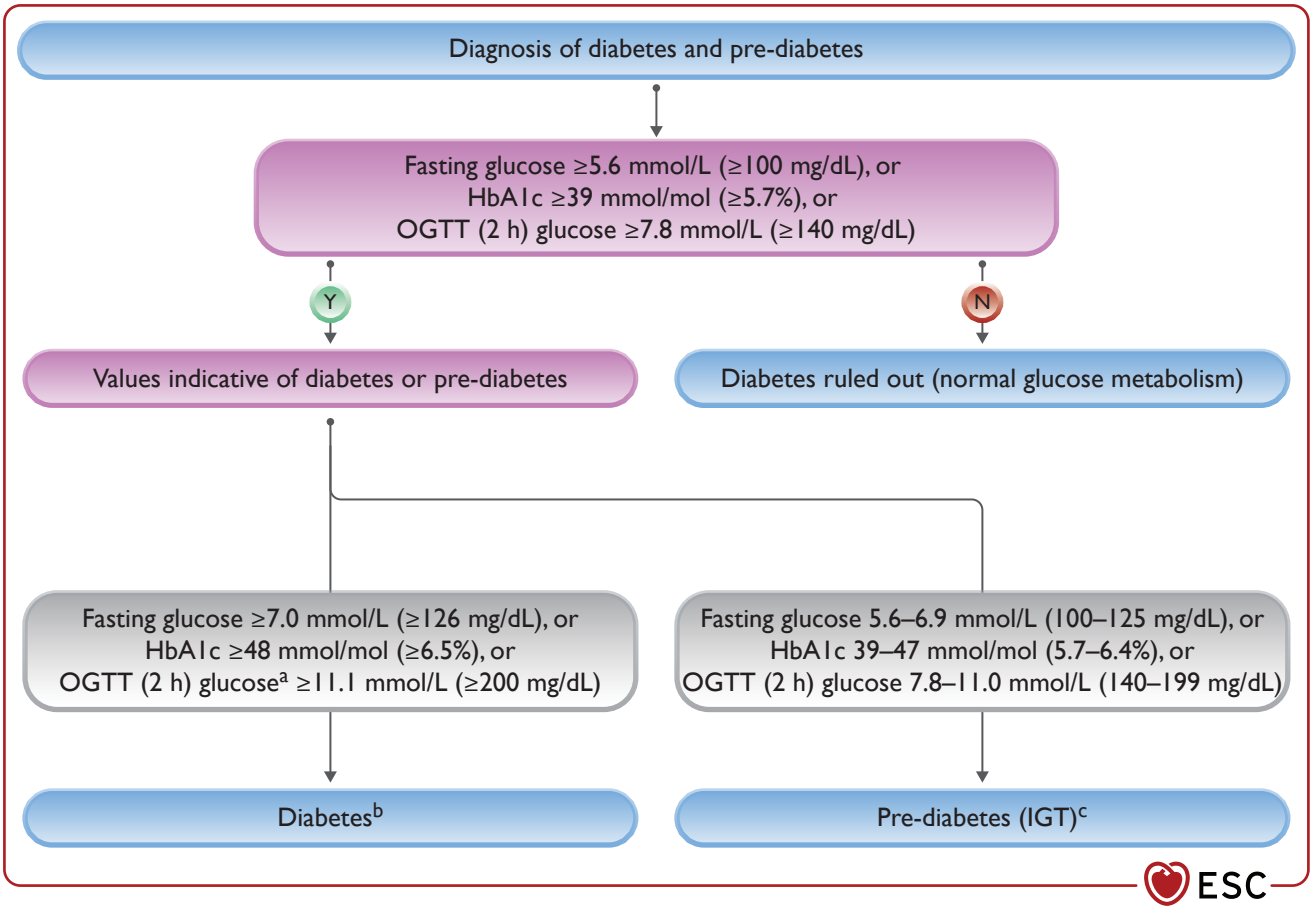

Figure 2 Diagnosis of diabetes and pre-diabetes. HbA1c, glycated haemoglobin; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test. [a]Rule out stress hyperglycaemia (often manifests as elevated glucose and normal HbA1c). [b]In the presence of symptoms, a single test is enough; in the absence of symptoms, two abnormal tests are required to make the diagnosis. [c]American Diabetes Association criteria are used in this scheme for the diagnosis of pre-diabetes.

acute pancreatic damage, HbA1c can lead to false-negative results. Another practical limitation is the lack of test availability in some parts of the world due to financial constraints.

Guidelines agree that HbA1c ≥48 mmol/mol (≥6.5%) is diagnostic of diabetes, while the diagnosis of pre-diabetes uses two different cut-off values. The WHO criteria define pre-diabetes as HbA1c 42–47 mmol/mol (6.0–6.4%), while the ADA recommends a wider range of 39–47 mmol/mol (5.7–6.4%).[5,7] Notably, the combination of HbA1c and fasting glucose in the diabetes range is diagnostic of diabetes and a second test is not required, even if the individual is asymptomatic. However, if the two are discordant, the number in the diabetes range should be repeated or, preferably, an OGTT performed, which remains the gold standard for diagnosing diabetes in unclear cases. The criteria used for diagnosing diabetes and pre-diabetes are summarized in *Table 6*. It should be noted that data from 73 studies on 294 998 individuals without known diabetes suggest that HbA1c is as good as or better than fasting, random, or post-load glucose levels for predicting CV risk.[14]

A diagram for the diagnosis of diabetes is shown in *Figure 2*.

3.2. Classifying diabetes

After abnormal glucose metabolism is diagnosed, the next step is to ascertain the type of diabetes in order to start the appropriate therapies (Supplementary data online, *Table S2*).

3.2.1. Type 1 diabetes

Type 1 diabetes constitutes 5–10% of individuals with diabetes and is secondary to destruction of pancreatic β-cells by an autoimmune process, with subsequent insulin deficiency. Recent guidance on diagnosing T1DM has been published.[13]

Briefly, individuals aged <35 years presenting with diabetes should be suspected of having T1DM, although this condition can occur at any age. A short history of osmotic symptoms accompanied by weight loss and raised glucose levels in a younger individual is highly suggestive of T1DM. Antibody testing helps to confirm the diagnosis, although this can be negative in 5–10% of individuals with T1DM, while C-peptide helps to assess endogenous insulin production in unclear cases (Supplementary data online, *Table S2*).

Pancreatic β-cell function can partially recover after the diagnosis of T1DM, and this can last several years, often referred to as the 'honeymoon period'. However, if this persists beyond 5 years, an alternative type of diabetes needs to be considered.[15] Of importance, the combination of T1DM with insulin resistance, which can be referred to as double diabetes (DD), increases the risk of vascular complications, although the exact definition of DD is yet to be determined.[16]

3.2.2. Type 2 diabetes

Type 2 diabetes is the most common cause of diabetes (90% of the diabetes population) and is usually caused by insulin resistance coupled with 'relative' insulin deficiency, resulting in raised glucose levels. Individuals with T2DM can be asymptomatic and can be diagnosed after presenting with CV complications (Supplementary data online, *Table S2*). Therefore, it is mandatory to screen all patients with CVD for the presence of diabetes.

3.2.3. Monogenic diabetes

This comprises many mutations that cause glucose mishandling. A full description can be found elsewhere.[17] Briefly, monogenic diabetes should be suspected in the presence of a strong family history of abnormal glucose metabolism in an autosomal dominant manner (i.e. successive generations with diabetes at a young age).[17]

Patients diagnosed with diabetes before the age of 6 months and those not fitting the T1DM or T2DM profiles should be suspected of having monogenic diabetes.

3.2.4. Secondary diabetes and stress hyperglycaemia

Diabetes can occur secondary to various conditions and therapies (Supplementary data online, *Table S2*). Stress hyperglycaemia is not uncommon in hospitalized patients and can occur in individuals with acute coronary syndrome (ACS) or HF.[18] Stress hyperglycaemia without diabetes is associated with adverse in-hospital outcomes, and should be suspected in those with raised glucose levels during admission and normal HbA1c.[19] Such individuals are best investigated using OGTT a few weeks after discharge to rule out diabetes or impaired glucose tolerance. Some studies suggest performing OGTT before hospital discharge but robust data supporting this approach are lacking.[20,21]

3.2.5. Gestational diabetes

Gestational diabetes mellitus (GDM) is defined as diabetes diagnosed in the second or third trimester of pregnancy that was not overt diabetes before gestation.[7] While there is still no worldwide consensus regarding the best testing strategy, the 'one-step' 75 g OGTT, also recommended by the WHO, is the preferred test in many countries.[22] In women with GDM, repeat testing is required in the postpartum period to rule out persistent abnormal glucose metabolism. Women with GDM will require lifelong annual diabetes screening given the high risk of developing diabetes.[23–25] Also, evidence suggests that women with a history of GDM are at increased CV risk, even with normal post-partum glucose levels. Given that GDM is an important precursor of future cardiometabolic complications, women with a history of GDM should regularly be screened not only for diabetes, but also for CV health.[26–29]

3.2.6. Further sub-group classification of type 2 diabetes

For information regarding further sub-group classification of T2DM, see Supplementary data online, *Section 1.1.1*.

3.3. Screening for diabetes

Criteria for diabetes testing differ widely across regions, and a comprehensive global screening programme is yet to be developed. It is generally agreed, however, that individuals in high-risk groups (those living with overweight or obesity, or having markers of insulin resistance, such as acanthosis nigricans or fatty liver disease) should be regularly screened, particularly after age 45 years. The ADA developed a relatively simple 7-point scoring system based on age, sex, weight, physical activity (PA), history of GDM, presence of hypertension, and family history of diabetes; it is advised that those scoring ≥5 are screened for diabetes.[7]

The prevalence of diabetes is increased among patients with CVD, with 23–37% of patients with ACS and 10–47% of patients with HF diagnosed with diabetes. This results in worse clinical outcomes compared with individuals with normal glucose metabolism.[30–33] Therefore, individuals with ASCVD and/or HF and/or AF, particularly those admitted to hospital with an acute event, should be tested for diabetes; those with suspected stress hyperglycaemia (raised glucose levels

during admission with normal HbA1c) should undergo post-discharge glucose testing, preferably with OGTT, to rule out persistent abnormal glucose metabolism.

Although OGTT has been previously advocated for diabetes screening in individuals with CVD, practicalities and low reproducibility of the test limited widespread use.[34,35] Importantly, evidence indicates that HbA1c, or fasting glucose, are stronger predictors of vascular complications than 2 h OGTT and it is therefore best to adopt these simple measures for general screening, particularly given their high reproducibility.[35–38]

Recommendation Table 1 — Recommendations for diagnosing diabetes

Recommendations	Class[a]	Level[b]
Screening for diabetes is recommended in all individuals with CVD,[c] using fasting glucose and/or HbA1c.[5–7,36,37,39]	I	A
It is recommended that the diagnosis of diabetes is based on HbA1c and/or fasting plasma glucose, or on an OGTT if still in doubt.[d,5–8,10,11]	I	B

CVD, cardiovascular disease; HbA1c, glycated haemoglobin; OGTT, oral glucose tolerance test.
[a]Class of recommendation.
[b]Level of evidence.
[c]Cardiovascular disease includes atherosclerotic cardiovascular disease, atrial fibrillation, and heart failure.
[d]Stress hyperglycaemia should be suspected in the presence of high glucose levels and normal HbA1c (see text for details).

4. Cardiovascular risk assessment in patients with type 2 diabetes

Individuals with T2DM are at a two- to four-fold higher risk of developing CVD during their lifetime alongside its manifestations CAD, stroke, HF, and AF, as well as peripheral artery diseases (PAD).[40,41] In addition, many patients with CVD have undiagnosed T2DM. Given that having diabetes and CVD, especially at a younger age, has a major impact on prognosis, it is of utmost importance to screen patients with CVD for diabetes and to assess CV risk in individuals with diabetes, and evaluate them for CV and kidney disease.[42]

4.1. Assessing cardiovascular risk in type 2 diabetes

When assessing CV risk in individuals with T2DM, it is important to consider medical and family history, symptoms, findings from examination, laboratory and other diagnostic test results, and the presence of ASCVD or severe TOD. There is not enough robust evidence to suggest that assessment of coronary artery calcium (CAC) or intima media thickness help reclassify CV risk in people with T2DM. Severe TOD is defined as:

(i) Estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2 irrespective of albuminuria, or
(ii) eGFR 45–59 mL/min/1.73 m^2 and microalbuminuria (urinary albumin-to-creatinine ratio [UACR] 30–300 mg/g; stage A2), or
(iii) Proteinuria (UACR >300 mg/g; stage A3), or
(iv) Presence of microvascular disease in at least three different sites (e.g. microalbuminuria (stage A2) plus retinopathy plus neuropathy; see *Section 9.1* for CKD screening).[43–45]

4.1.1. Cardiovascular risk categories in type 2 diabetes

Individuals with T2DM should be categorized into different CV risk groups based on the following criteria (*Table 7*):

Table 7 Cardiovascular risk categories in type 2 diabetes

Very high CV risk	Patients with T2DM with: • Clinically established ASCVD or • Severe TOD or • 10-year CVD risk ≥20% using SCORE2-Diabetes
High CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk 10 to <20% using SCORE2-Diabetes
Moderate CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk 5 to <10% using SCORE2-Diabetes
Low CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk <5% using SCORE2-Diabetes

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; SCORE2-Diabetes, type 2 diabetes-specific 10-year CVD risk score; T2DM, type 2 diabetes mellitus; TOD, target-organ damage; UACR, urinary albumin-to-creatinine ratio.
Severe TOD defined as eGFR <45 mL/min/1.73 m^2 irrespective of albuminuria; or eGFR 45–59 mL/min/1.73 m^2 and microalbuminuria (UACR 30–300 mg/g; stage A2); or proteinuria (UACR >300 mg/g; stage A3); or presence of microvascular disease in at least three different sites [e.g. microalbuminuria (stage A2) plus retinopathy plus neuropathy].[43–45]

4.1.2. SCORE2-Diabetes: estimating 10-year cardiovascular disease risk

In patients aged ≥40 years with T2DM without ASCVD or severe TOD, it is recommended to estimate 10-year CVD risk using the SCORE2-Diabetes algorithm (*Figure 3*). In these patients, risk factors for ASCVD should be evaluated on an individual basis. In the 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice, the ADVANCE (Action in Diabetes and Vascular disease: preterAx and diamicroN MR Controlled Evaluation) or DIAL (Diabetes lifetime-perspective prediction) models were suggested for estimating CVD risk among patients with diabetes.[46–48] However, these models have some limitations for use in Europe, as they do not allow for substantial variations of risk across countries, meaning they may misestimate risk in these circumstances. Furthermore, these models have been developed from a narrow set of studies and have not been systematically 'recalibrated' (i.e. statistically adapted) to contemporary CVD rates, meaning they are not ideal for use in contemporary European populations. To address these limitations, the current Guidelines recommend use of the SCORE2-Diabetes model, which extends the regionally recalibrated European SCORE2 10-year risk model to enable use in individuals with T2DM aged 40–69 years without ASCVD or severe TOD, and to estimate an individual's 10-year risk of fatal and non-fatal CVD events (MI, stroke).[49]

SCORE2-Diabetes integrates information on conventional CVD risk factors (i.e. age, smoking status, systolic blood pressure [SBP], and total and high-density lipoprotein [HDL]-cholesterol) with diabetes-specific information (e.g. age at diabetes diagnosis, HbA1c, and eGFR).[50] This model is calibrated to four clusters of countries (low, moderate, high, and very high CVD risk) using the similar methodology of the

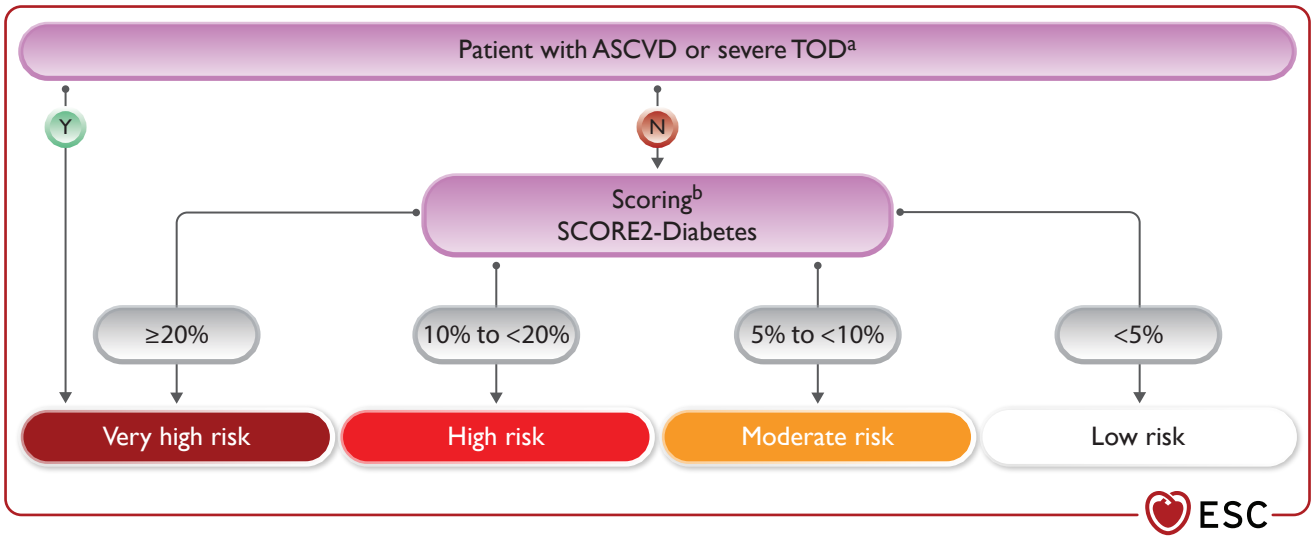

Figure 3 Cardiovascular risk categories in patients with type 2 diabetes. ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease risk; eGFR, estimated glomerular filtration rate; TOD, target-organ damage; UACR, urinary albumin-to-creatinine ratio. [a]Severe TOD defined as eGFR <45 mL/min/1.73 m^2 irrespective of albuminuria; or eGFR 45–59 mL/min/1.73 m^2 and microalbuminuria (UACR 30–300 mg/g; stage A2); or proteinuria (UACR >300 mg/g; stage A3), or presence of microvascular disease in at least three different sites [e.g. microalbuminuria (stage A2) plus retinopathy plus neuropathy].[43–45] [b]The thresholds (10-year CVD risk) suggested are not definitive but rather designed to prompt joint decision-making conversations with patients about intensity of treatment, as well as additional interventions. SCORE2-Diabetes refers to patients aged ≥40 years.

SCORE2 and SCORE2-Older Persons (SCORE2-OP) algorithms (Supplementary data online, *Section 2*; *Table S3*).[49,51]

The ESC CVD Risk Calculation App includes SCORE2-Diabetes to facilitate risk estimation and communication between health professionals and individuals with T2DM (Supplementary data online, *Tables S4–6*).

Additional risk scores that attempt to estimate lifetime risk in individuals with diabetes (such as the DIAL2 [DIAbetes Lifetime] model, which is calibrated to different European countries) can also be used to aid treatment decisions.[52] However, estimation of lifetime risk should be adapted as new methods become available in the future.

Thresholds for the different risk categories are shown in *Table 7* and *Figure 3*. In general, no risk threshold is universally applicable, and the risk thresholds suggested in these Guidelines for use with SCORE2-Diabetes should be used to help guide clinicians and patients to prompt joint decision-making conversations for considering the intensity of treatment and additional interventions to prevent ASCVD (such as lipid-lowering therapies [*Section 5.5*] or SGLT2 inhibitors and/or GLP-1 RAs [*Section 5.3*]). However, 10-year risk thresholds are for guidance only and other patient characteristics may lead to decisions to treat or not treat irrespective of such thresholds.

Recommendation Table 2 — Recommendations for assessing cardiovascular risk in patients with type 2 diabetes

Recommendations to assess cardiovascular risk in patients with diabetes	Class[a]	Level[b]
It is recommended to screen patients with diabetes for the presence of severe TOD.[c,43,44]	I	A
It is recommended to assess medical history and the presence of symptoms suggestive of ASCVD in patients with diabetes.[53–55]	I	B
In patients with T2DM without symptomatic ASCVD or severe TOD,[c] it is recommended to estimate 10-year CVD risk via SCORE2-Diabetes.[d,50]	I	B

ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; SCORE2-Diabetes, type 2 diabetes-specific 10-year ASCVD risk score; T2DM, type 2 diabetes mellitus; TOD, target-organ damage; UACR, urinary albumin-to-creatinine ratio.
[a]Class of recommendation.
[b]Level of evidence.
[c]Severe TOD defined as eGFR <45 mL/min/1.73 m^2 irrespective of albuminuria; or eGFR 45–59 mL/min/1.73 m^2 and microalbuminuria (UACR 30–300 mg/g; stage A2); or proteinuria (UACR >300 mg/g; stage A3); or presence of microvascular disease in at least three different sites (e.g. microalbuminuria (stage A2) plus retinopathy plus neuropathy).
[d]SCORE2-Diabetes refers to patients aged ≥40 years. In patients with T2DM without ASCVD and/or severe TOD, with age <40 years, risk factors for ASCVD should be evaluated on an individual basis.

5. Cardiovascular risk reduction in patients with diabetes: targets and treatments

5.1. Lifestyle and diabetes

Lifestyle changes are recommended as the basic measure for preventing and managing T2DM.[48] Advice should be addressed by a multifactorial approach with patient-centred communication adapted to the health status and health literacy of the patient (*Section 5.7*). In T2DM, as investigated in the Action for Health in Diabetes trial (Look AHEAD; 5145 T2DM patients, 59% female, mean age 58 years, mean body mass index [BMI] 36 kg/m^2), lifestyle intervention by nutritional counselling, meal replacement, and exercise induced an average of 8.6% weight loss, which was associated with a significant reduction in HbA1c and BP.[56] Effects on weight and risk-factor control diminished after 5 years in those with low adherence to the lifestyle programme.[56] After 10 years, CV events (i.e. a composite endpoint of CV death, non-fatal MI, non-fatal stroke, and hospitalization for angina) were not different to usual

care.[56] However, microvascular disease complications (i.e. development of CKD) were significantly reduced (hazard ratio [HR] 0.69; 95% confidence interval [CI], 0.55–0.87; $P = 0.002$) by lifestyle intervention, an effect associated with improvements in CV risk factors.[57] Additional analyses 16.7 years after the start of the study (9.6 years of intervention and then observation) revealed that participants who lost ≥10% of weight at 1 year of intervention had a 21% reduced risk of mortality (HR 0.79; 95% CI, 0.67–0.94; $P = 0.007$).[58] The decline in body fat mass was significantly associated with a lower risk of HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF), while a decline in waist circumference was only significantly associated with a lower risk of HFpEF.[59] In addition, baseline cardio-pulmonary fitness was associated with reduced risks of mortality and CV events during follow-up of 9.2 years.[60]

The DiRECT (Diabetes Remission Clinical Trial)—an open-label, cluster-randomized trial in patients with T2DM—assigned practices to provide either a weight-management programme including exercise (intervention group) or best-practice care by guidelines (control group). At 12 months, almost half of the participants in the intervention group achieved remission to a non-diabetic state and were off glucose-lowering drugs.[61] Home-based exercise intervention in patients with CAD and T2DM (ARTEMIS study; Finnish randomized controlled trial [RCT]; $n = 127$; 2-year controlled, home-based exercise training vs. usual care), however, did not significantly improve CV risk factors despite significant improvements in exercise capacity ($P = 0.030$).[62]

5.1.1. Weight reduction

In patients with obesity and T2DM, reducing weight is one of the cornerstones of treatment.[63] Weight loss of >5% improves glycaemic control, lipid levels, and BP in overweight and obese adults with T2DM.[64,65] These effects can be achieved by improving energy balance and/or introducing obesity medications. Orlistat, naltrexone/bupropion, and phentermine/topiramate are each associated with achieving >5% weight loss at 52 weeks compared with placebo.[66] However, glucose-lowering agents such as GLP-1 RAs, the dual agonist tirzepatide, and SGLT2 inhibitors also significantly reduce body weight.[67,68] Adding exercise to a GLP-1 RA (liraglutide) had a greater effect on weight reduction and maintenance.[69] Comparing the effects on weight reduction between GLP-1 RAs and SGLT2 inhibitors, the former seems to be superior. Given the additional beneficial effects of GLP-1 RAs and SGLT2 inhibitors on CV outcomes in T2DM (*Section 5.3*), these agents should be the preferred glucose-lowering medication in overweight and obese patients with CVD and T2DM, as obesity medications have, to date, not shown to reduce CV events.[70–72]

If weight is not managed effectively by lifestyle interventions and medication, bariatric surgery should be considered in patients with T2DM and a BMI ≥35 kg/m^2 (≥Class II; WHO classification) to achieve long-term weight loss, reduce blood glucose, and improve CV risk factors. Data from the Swedish Obesity Subjects (SOS) study revealed that after 24-year follow-up, bariatric surgery was associated with a prolonged life expectancy compared with lifestyle and intensive medical management alone.[73,74] The corresponding HR was 0.70 (95% CI, 0.57–0.85) for CV death and 0.77 (95% CI, 0.61–0.96) for death from cancer.[75,76] This evidence has been extended to patients with CVD and obesity, as a large case-control study ($n = 2638$) revealed that bariatric surgery was also associated with a lower incidence of major adverse cardiovascular events (MACE) in those patients.[77] Still, potential adverse events after bariatric surgery should also be considered.[78]

Recommendation Table 3 — Recommendations for reducing weight in patients with type 2 diabetes with or without cardiovascular disease

Recommendations	Class[a]	Level[b]
It is recommended that individuals living with overweight or obesity aim to reduce weight and increase physical exercise to improve metabolic control and overall CVD risk profile.[56,79]	I	A
Glucose-lowering medications with effects on weight loss (e.g. GLP-1 RAs) should be considered in patients with overweight or obesity to reduce weight.[67]	IIa	B
Bariatric surgery should be considered for high and very high risk patients with BMI ≥35 kg/m^2 (≥Class II[c]) when repetitive and structured efforts of lifestyle changes combined with weight-reducing medications do not result in maintained weight loss.[73–77]	IIa	B

BMI, body mass index; CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist.
[a]Class of recommendation.
[b]Level of evidence.
[c]World Health Organization classification.

5.1.2. Change in diet or nutrition

In general, patients with T2DM should follow nutritional recommendations that reduce body weight and improve metabolic control and outcomes.[48] A Mediterranean-style eating pattern improves glycaemic control, lipids, and BP.[80,81] If this diet is supplemented with olive oil or nuts, as in the non-randomized PREvencion con Dieta MEDiterranea (PREDIMED) study in individuals at high CV risk (49% T2DM), the risk of ASCVD was reduced by 28–31%.[82] Recent data from the Coronary Diet Intervention With Olive Oil and Cardiovascular Prevention (CORDIOPREV) study confirmed the benefit of a Mediterranean diet by showing that male patients with established CAD benefitted more from a Mediterranean diet than from a low-fat diet intervention after 7 years of follow-up. A shift from a more animal-based to a plant-based food pattern may also reduce ASCVD risk.[83–85]

Data from studies on supplementation with n–3 fatty acids do not support recommending n–3 fatty acid supplements for secondary prevention of CVD in T2DM.[86,87] The consumption of sugars, sugar-sweetened soft drinks, and fruit juices should be avoided.[88,89] Moreover, alcohol intake should generally be moderate, as any amount of alcohol uniformly increases BP and BMI.[90–92] A high-protein diet (30% protein, 40% carbohydrates, and 30% fat) seems to be superior to a standard-protein diet (15% protein, 55% carbohydrates, and 30% fat) in overweight and obese (mean weight 107.8 ± 20.8 kg) patients with HF; both diets were equal in reducing body weight (3.6 vs. 2.9 kg, respectively) and waist circumference (1.9 vs. 1.3 cm, respectively), but the high-protein diet resulted in greater reductions in CV risk factors, e.g. HbA1c, cholesterol, triglycerides, and BP.[93]

People with CVD and T2DM are encouraged to reduce sodium intake, as this may reduce systolic BP by, on average, 5.8 mmHg in hypertensive patients and 1.9 mmHg in normotensive patients.[94,95] In a meta-analysis, in hypertensive and normotensive people, reducing salt intake by 2.5 g/day resulted in a 20% relative reduction of ASCVD events.[95] In addition, salt substitution with reduced sodium levels and increased potassium levels has been shown to reduce stroke, CVD, and overall mortality in patients with high CV risk.[96]

Recommendation Table 4 — Recommendations for nutrition in patients with type 2 diabetes with or without cardiovascular disease

Recommendations	Class[a]	Level[b]
It is recommended to adopt a Mediterranean or plant-based diet with high unsaturated fat content to lower cardiovascular risk.[82,85]	I	A

[a]Class of recommendation.
[b]Level of evidence.

5.1.3. Increasing physical activity and exercise

Regular moderate to vigorous PA has favourable effects on metabolic control and CV risk factors in T2DM.[97–100] Intervention programmes reduce HbA1c by 0.6% in patients with T2DM, with the combination of endurance and resistance exercise having the most beneficial effects.[101] Moreover, compared with low total PA, high total PA is associated with a lower CV mortality risk, as well as a reduction in all-cause mortality (all-cause mortality: HR 0.60 [95% CI, 0.49–0.73], comparing high vs. low total PA).[97]

Structured exercise intervention is also recommended in patients with T2DM with established CVD (e.g. CAD, AF, HFpEF; heart failure with mildly reduced ejection fraction [HFmrEF]; HFrEF).[102–104] Interval endurance exercise training of more vigorous intensity (e.g. interval walking, alternating between moderate to vigorous intensities) has superior effects compared with moderate-intensity continuous walking regarding body weight, waist circumference, and glucose control.[105] Before starting a structured exercise programme in patients with T2DM and established CVD, performing a maximal exercise stress test to assess CV pathologies should be considered. Moreover, assessment of aerobic and anaerobic thresholds by spiroergometry is particularly useful to provide an individualized endurance exercise prescription including exercise intensity.[106–108] Optimal intensity is determined based on an individual's maximum (peak) effort during spiroergometry, e.g. percentage of cardiorespiratory fitness (% peak oxygen consumption), percentage of maximum (peak) heart rate (% HR_{max}), or perceived exertion rate according to the Borg scale.[107–109] Exercise prescription is recommended to be adapted to T2DM-associated comorbidities, e.g. CAD, HF, AF, diabetic peripheral neuropathy, or retinopathy, as well as age and frailty.[104,107,108] Resistance exercise is recommended to be performed at least twice weekly (intensity of 60–80% of the individual's one-repetition maximum). For older or deconditioned adults, less volume and lower intensities are recommended, particularly during the initiation phase of 3–6 weeks.[106]

Interventions are based on encouraging an increase in any PA, as even small amounts were shown to have beneficial effects; even an extra 1000 steps of walking per day is advantageous and may be a good starting point for many patients.[98,100] Moreover, a gradual increase in activity level is recommended. Structured exercise should be additionally introduced at the start or after first achievements to increase activity. Patients should perform ≥2 sessions per week of endurance exercise and/or resistance exercise training. PA accumulated in bouts of even <10 min is associated with favourable outcomes, including reduced mortality.[110,111]

Interventions shown to increase PA level or reduce sedentary behaviour include behaviour theory-based interventions, such as goal-setting, re-evaluation of goals, self-monitoring, and feedback.[112,113] Using a wearable activity tracker (e.g. smartphones) may help increase PA.[114] Most important is to encourage PA that people enjoy and/or can include in their daily routines, as such activities are more likely to be feasible and sustainable.

Recommendation Table 5 — Recommendations for physical activity/exercise in patients with type 2 diabetes with or without cardiovascular disease

Recommendation	Class[a]	Level[b]
It is recommended to increase any physical activity (e.g. 10 min daily walking) in all patients with T2DM with and without CVD. Optimal is a weekly activity of 150 min of moderate intensity or 75 min of vigorous endurance intensity.[97,98]	I	A
It is recommended to adapt exercise interventions to T2DM-associated comorbidities, e.g. frailty, neuropathy, or retinopathy.[108,115]	I	B
It is recommended to introduce structured exercise training in patients with T2DM and established CVD, e.g. CAD, HFpEF, HFmrEF, HFrEF, or AF to improve metabolic control, exercise capacity and quality of life, and to reduce CV events. [108,115,116]	I	B
It is recommended to perform resistance exercise in addition to endurance exercise at least twice a week.[115,117]	I	B
The use of behavioural theory-based interventions, such as goal-setting, re-evaluation of goals, self-monitoring, and feedback, should be considered to promote physical activity behaviour.[112,113]	IIa	B
It should be considered to perform a maximally tolerated exercise stress test in patients with T2DM and established CVD before starting a structured exercise programme.	IIa	C
It may be considered to use wearable activity trackers to increase physical activity behaviour.[114]	IIb	B

AF, atrial fibrillation; CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular disease; HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; T2DM, type 2 diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.

5.1.4. Smoking cessation

Smoking cessation is a key lifestyle intervention in patients with T2DM with or without CVD with evidence suggesting a 36% reduction in mortality in CVD patients.[118–120] If advice, encouragement, and motivation are insufficient, then drug therapies should be considered early, including nicotine replacement therapy (chewing gum, transdermal nicotine patches, nasal spray, inhaler, sublingual tablets) followed by bupropion.[121] In patients with ASCVD, varenicline, bupropion, telephone therapy, and individual counselling all increase success rates.[122] Electronic cigarettes (e-cigarettes) have been addressed as a potential smoking cessation aid to bridge transition from smoking to abstention, but—if used at all—should be limited for a short period of time. A consensus regarding the efficacy and safety for this approach has yet to be reached.[123,124] Overall, smoking cessation programmes have low efficacy at 12 months; nonetheless, cessation measures should be repetitively addressed for smoking abstention to succeed.[125]

The assessment of lifestyle risk-factor components and stepwise lifestyle recommendations in patients with CVD and diabetes is summarized in more detail in *Section 5.7*.

Recommendation Table 6 — Recommendations for smoking cessation in patients with type 2 diabetes with or without cardiovascular disease

Recommendations	Class[a]	Level[b]
It is recommended to stop smoking to reduce cardiovascular risk.[118–120]	I	A
Nicotine replacement therapy, varenicline, and bupropion, as well as individual or telephone counselling, should be considered to improve smoking cessation success rate.[121]	IIa	B

[a]Class of recommendation.
[b]Level of evidence.

5.2. Glycaemic targets

5.2.1. Role of glycated haemoglobin

Reducing HbA1c decreases microvascular complications, particularly when achieving near-normal levels (HbA1c <7%, <53 mmol/mol), but the effects on macrovascular disease are more complex.[126–129] The DCCT (Diabetes Control and Complications Trial) in T1DM and the UKPDS (United Kindom Prospective Diabetes Study) in newly diagnosed T2DM have shown that reducing HbA1c decreases long-term macrovascular events without having a significant effect in the medium term of 6.5–10.0 years.[130–132] Other studies, such as ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation), ACCORD (Action to Control Cardiovascular Risk in Diabetes), and VADT (Veterans Affairs Diabetes Trial), including higher-risk T2DM cohorts, have similarly failed to show an effect for intensive glycaemic control on short/medium-term macrovascular risk (over 3.5–5.6 years). Meta-analyses of the UKPDS, ADVANCE, ACCORD, and VADT studies, including 27 049 participants, have demonstrated that lowering HbA1c reduces MACE, driven by a reduction in MI (HF and stroke risk were unaffected), and decreases microvascular complications (renal and retinal but not neuropathy).[133,134]

Of interest, the ACCORD trial, with 35% of participants having a previous CV event, showed increased mortality (HR 1.22; 95% CI, 1.01–1.46; $P = 0.04$) in the intensive glycaemic arm (HbA1c 6.5%, 48 mmol/mol) compared with controls.[129] Also, observational studies have shown a U-shaped relationship between HbA1c and clinical outcome, suggesting that lower HbA1c is not always better.[135,136]

5.2.2. Additional glycaemic targets

Hypoglycaemia is associated with an increased risk of vascular events, explaining recent consensus advocating hypoglycaemic exposure at <1% (i.e. <15 min/day) in individuals at high CV risk.[137,138] A causal relationship between hypoglycaemia and adverse outcomes is not always clear as low glucose levels can be a marker of ill health.[139,140]

In addition to hypoglycaemia, glycaemic variability is emerging as a potential vascular risk factor, but studies are limited and more research in this area is warranted.

Post-prandial glucose has been suggested to independently predict vascular disease, even in individuals without a previous history of diabetes.[141] However, manipulating prandial glucose levels failed to impact clinical outcome, and therefore, this remains an unresolved area.[142,143]

5.2.3. Glycaemic control following vascular events

Hyperglycaemia following ACS is associated with worse clinical outcome.[144] The DIGAMI 1 (Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction) trial demonstrated reduced mortality with intensive glucose control post-ACS, but DIGAMI 2, which was underpowered, failed to confirm these findings.[145,146] Unexpectedly, DIGAMI 2 showed a numerical increase in mortality in the intervention arm, particularly in insulin-treated patients, suggesting an adverse role for hypoglycaemia in this population.[147] Therefore, large-scale glycaemic studies are required, using continuous glucose monitoring (CGM) to assess glucose levels, to establish whether optimizing glycaemia in patients with CVD and diabetes improves clinical outcome.

In summary, glucose control in individuals with diabetes at high CV risk is a complex area and current evidence indicates the need to address multiple glycaemic measures, including personalizing HbA1c targets, minimizing hypoglycaemic exposure, and limiting glucose variability. *Figure 4* provides a simple guide to glycaemic control in patients with T2DM and CVD.

Recommendation Table 7 — Recommendations for glycaemic targets in patients with diabetes

Recommendations	Class[a]	Level[b]
It is recommended to apply tight glycaemic control (HbA1c <7%) to reduce microvascular complications.[126–128,133]	I	A
It is recommended to avoid hypoglycaemia, particularly in patients with CVD.[134–137,147]	I	B
It is recommended to individualize HbA1c targets according to comorbidities, diabetes duration, and life expectancy.[134,137]	I	C
Tight glycaemic control should be considered for reducing CAD in the long term, preferably using agents with proven CV benefit.[c,129–132]	IIa	B

CAD, coronary artery disease; CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; s.c. subcutaneous; SGLT2, sodium–glucose co-transporter-2.
[a]Class of recommendation.
[b]Level of evidence.
[c]SGLT2 inhibitors (empagliflozin, canagliflozin, dapagliflozin, sotagliflozin) or GLP-1 RAs (liraglutide, semaglutide s.c., dulaglutide, efpeglenatide).

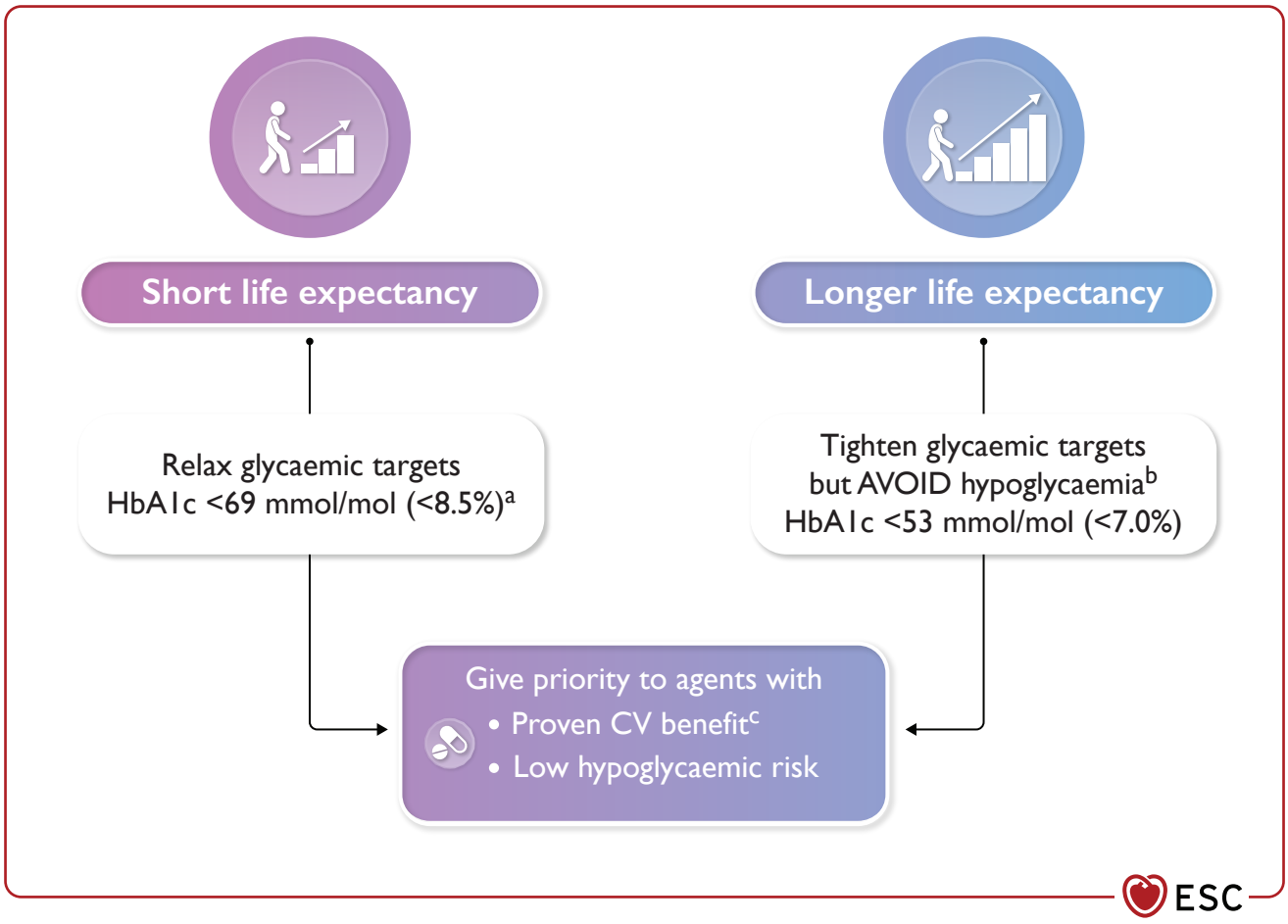

Figure 4 Simple guide to glycaemic targets in patients with type 2 diabetes and cardiovascular disease. CV, cardiovascular; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin, s.c., subcutaneous; SGLT2, sodium–glucose co-transporter-2. [a]Adjust target in the presence of hyperglycaemic symptoms (polyuria and polydipsia). [b]Hypoglycaemia is usually a concern only in those on a sulphonylurea and/or insulin. [c]SGLT2 inhibitors (empagliflozin, canagliflozin, dapagliflozin, sotagliflozin) or GLP-1 RAs (liraglutide, semaglutide s.c., dulaglutide, efpeglenatide).

5.3. Atherosclerotic cardiovascular disease risk reduction by glucose-lowering medications in diabetes

T2DM is common among patients with ASCVD or at the highest risk of CVD. The converse is also true: ASCVD is common in patients with T2DM.[148] Given these relationships, it is key to consider the presence of T2DM when deciding strategies to mitigate CV risk. It is imperative that the first step in this process is to screen all patients with CVD for T2DM. Many decisions are independent of glucose management, therefore, T2DM status can inform clinical decision-making for mitigating CV risk, as discussed for several other interventions in the current Guidelines.[149] Capitalizing on the results of multiple dedicated CVOTs of glucose-lowering medications in patients with diabetes and ASCVD or at high CV risk, there is now a wealth of data to inform the preferential use of selected glucose-lowering medications to reduce CV risk, independent of glucose management considerations. Glucose-lowering medications can be prescribed with two parallel, mutually exclusive intentions: (i) to improve CV outcomes and safety; and (ii) to control glucose. On this basis, in the current Guidelines, we have separated prescribing recommendations into those intended to improve CV outcomes and those intended to control glucose. Underpinning these recommendations are results from the key CVOTs delineating the efficacy and safety of glucose-lowering therapies for treating T2DM and their effect on CV outcomes.

5.3.1. Glucose-lowering medications with cardiovascular efficacy demonstrated in dedicated cardiovascular outcomes trials

5.3.1.1. Sodium–glucose co-transporter-2 inhibitors

The results of six CVOTs with SGLT2 inhibitors and one trial of a dual SGLT1/2 inhibitor have been published, comprising the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose) trial, the CANVAS (Canagliflozin Cardiovascular Assessment Study) programme (two trials combined for analyses), the DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis In Myocardial Infarction 58) trial, the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial, the VERTIS CV (eValuation of ERTugliflozin efflcacy and Safety CardioVascular Outcomes) trial, and the SCORED (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk) trial (Supplementary data online, *Table S7*).[71,150–154]

A meta-analysis of the six SGLT2 inhibitor trials demonstrated a reduction in the primary ASCVD-based composite of time to first event of CV death, MI, or stroke (MACE). This was most apparent in patients with established ASCVD (*Figure 5*).[155] Of note, neither dapagliflozin nor

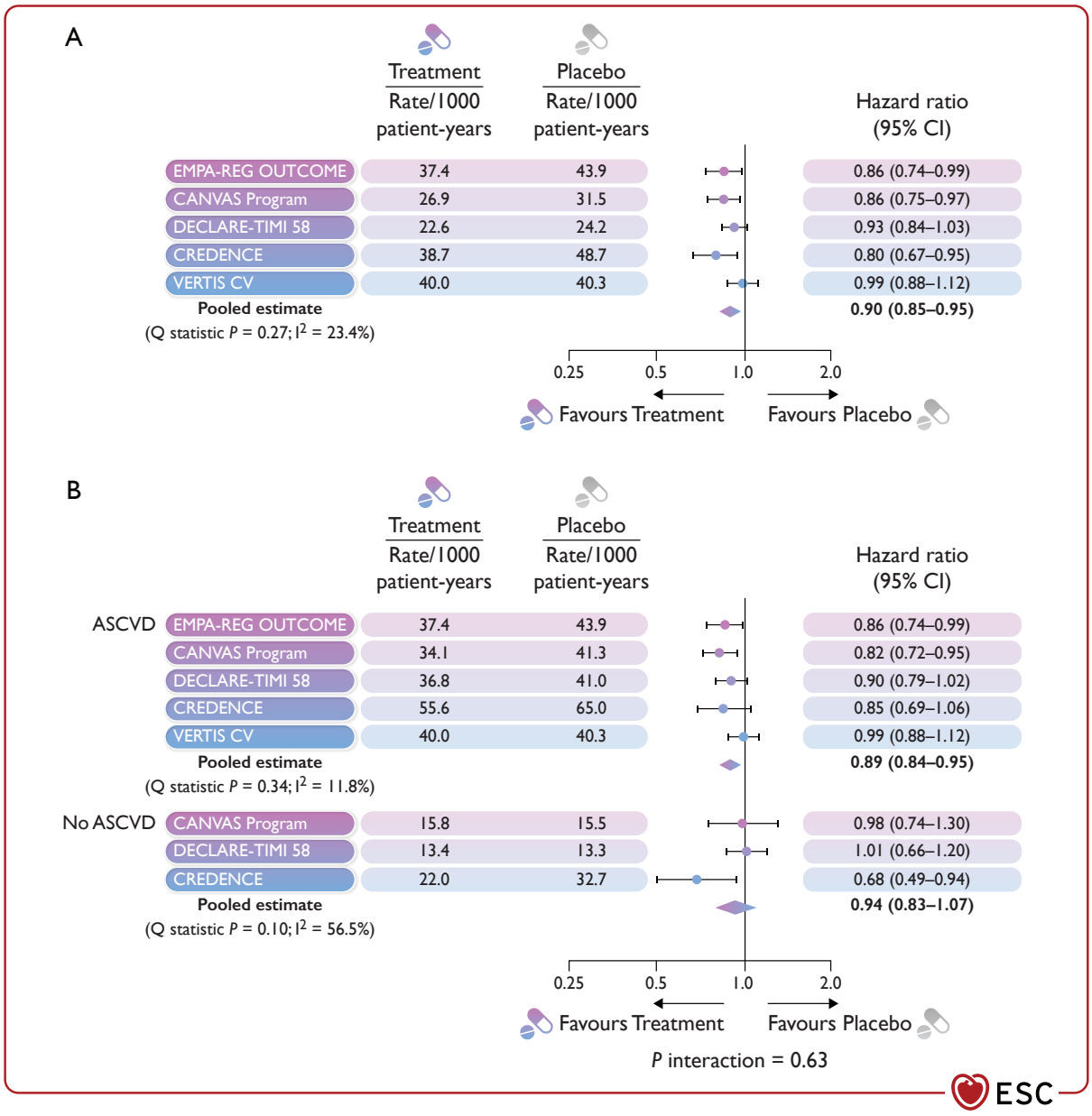

Figure 5 Meta-analysis of cardiovascular outcomes trial results of sodium–glucose co-transporter-2 inhibitors among patients with type 2 diabetes with or at high risk for atherosclerotic cardiovascular disease. (A) Overall major adverse cardiovascular events; (B) Major adverse cardiovascular events by atherosclerotic cardiovascular disease status. ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; Figure adapted from McGuire *et al.* 2021.This is an open access article distributed under the terms of the CC-BY-NC-ND License https://creativecommons.org/licenses/by-nc-nd/4.0/ [155]

ertugliflozin reduced the risk of MACE, but both reduced risk of HF hospitalization, with consistency across the class for HF benefits (*Section 7*). Based on these aggregate results, along with the GLP-1 RAs (see below), SGLT2 inhibitors are a preferred glucose-lowering therapy for patients with T2DM with ASCVD, independent of glucose control considerations, and independent of background metformin use.

Results from the meta-analysis demonstrated no statistically significant benefit for risk of MACE in the subsets of patients without ASCVD but with multiple ASCVD risk factors; yet the point estimate remains favourable in this subset, with no significant interaction by ASCVD status ($P = 0.63$; *Figure 5*). In patients with T2DM without ASCVD or severe TOD but with a calculated 10-year CVD risk ≥10% in the SCORE2-Diabetes algorithm (*Section 4.1*), treatment with SGLT2 inhibitors and/or GLP-1 RAs may be considered to reduce CV risk, independent of glucose control considerations. This recommendation is a consensus within the Task Force based on the assumption that some level of predicted CVD risk appears to be equivalent to 'severe TOD risk', acknowledging it is a Level C recommendation. Of note, it is in line with recommendations from EASD and ADA.[1,156,157]

5.3.1.2. Glucagon-like peptide-1 receptor agonists

Eight randomized, placebo-controlled CVOTs have examined the CV safety and efficacy of GLP-1 RAs in patients with T2DM with or at high risk of ASCVD. These trials comprise the ELIXA (Evaluation of

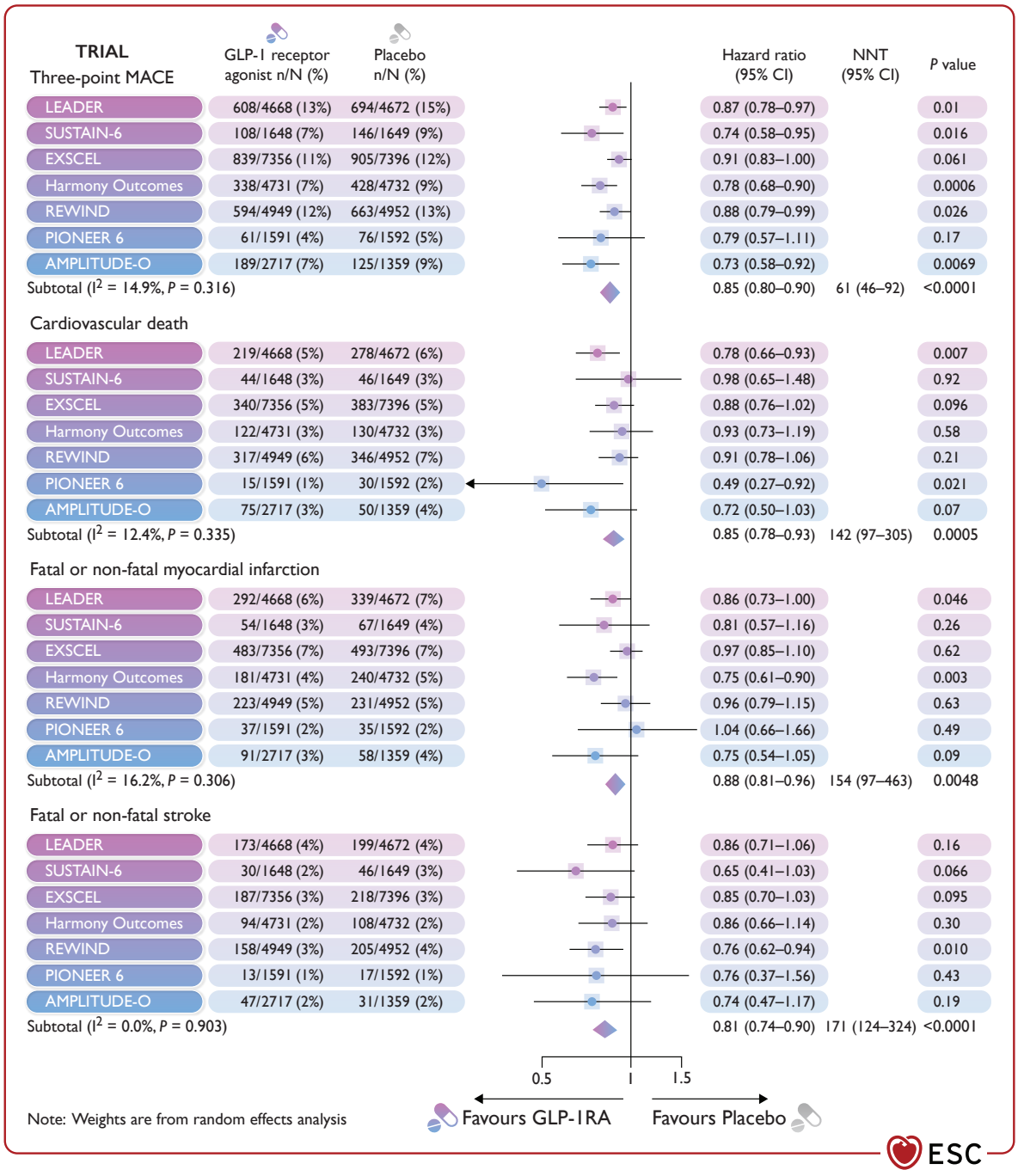

Figure 6 Meta-analysis of cardiovascular outcomes trials with glucagon-like peptide-1 receptor agonists (sensitivity analysis removing ELIXA). Risk of major adverse cardiovascular events and its components. CI, confidence interval; GLP-1, glucagon-like peptide-1; MACE, major adverse cardiovascular outcomes; NNT, number needed to treat. Figure adapted from Sattar *et al.* 2021.Reprinted from the Lancet with permission from Elsevier.[164]

Lixisenatide in Acute Coronary Syndrome) trial, the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial, the SUSTAIN 6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) trial, the EXSCEL (Exenatide Study of Cardiovascular Event Lowering) trial, the HARMONY Outcomes (Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus) trial, the REWIND (Researching Cardiovascular Events With a Weekly Incretin in Diabetes) trial, the PIONEER 6 (Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes) trial, and the AMPLITUDE-O (Effect of Efpeglenatide on Cardiovascular Outcomes) trial (Supplementary data online, *Table S8*).[70,72,158–163]

Five of the eight GLP-1 RAs tested demonstrated superior CV outcomes on the primary composite of time to the first event of CV death,

MI, and stroke compared with placebo. A meta-analysis of seven of the eight completed GLP-1 RA trials, excluding the ELIXA trial results (due to a very short pharmacodynamic half-life [3 h] of once a day [o.d.] lixisenatide, and the very high-risk population post-ACS differentiating it from all others), showed that a pooled estimate for GLP-1 RA vs. placebo for the primary outcome was reduced by 15% (HR 0.85; 95% CI, 0.80–0.90; *Figure 6*).[164] Results from pooled analyses of the effects of GLP-1 RA vs. placebo on individual CV outcomes included CV death (HR 0.85; 95% CI, 0.78–0.93), MI (HR 0.88; 95% CI, 0.81–0.96), stroke (HR 0.81; 95% CI, 0.74–0.90), and hospitalization for HF (HR 0.88; 95% CI, 0.79–0.98). Notably, the point estimate in the seven trials was lower (HR = 0.85) in those with established ASCVD than in those without (HR = 0.94), with $P_{int} = 0.068$, suggesting but not conclusively proving that GLP-1 RAs may reduce risks more in those with established ASCVD. As absolute risks are greater in those with established CV disease, the absolute benefits are also expected to be greater.

Based on these aggregate results, along with the SGLT2 inhibitors (see above) GLP-1 RAs are a preferred glucose-lowering therapy for patients with T2DM and ASCVD, independent of glucose control considerations, and independent of background metformin use. In patients with T2DM without ASCVD or severe TOD, but with a calculated 10-year CVD risk ≥10% in the SCORE2-Diabetes algorithm (*Section 4*), treatment with GLP-1 RAs and/or SGLT2 inhibitors may be considered to reduce CV risk, independent of glucose control considerations. This recommendation is a consensus within the Task Force based on the assumption that some level of predicted CVD risk appears to be equivalent to 'severe TOD risk', acknowledging it is a Level C recommendation. Of note, it is in line with recommendations from EASD and ADA.[1,156,157]

5.3.1.3. Pioglitazone

The PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) randomized CVOT assessed the CV effects of the thiazolidinedione (TZD) pioglitazone vs. placebo, independent of glucose control, in patients with T2DM and ASCVD. It failed to achieve statistical significance for its primary composite outcome of all-cause death, MI, stroke, unstable angina, coronary or peripheral revascularization, and amputation (HR 0.90; 95% CI, 0.80–1.02).[165] However, for the principal secondary outcome evaluating the gold-standard, three-point composite outcome of CV death, MI, and stroke, there was a nominally significant 16% relative risk (RR) reduction (HR 0.84; 95% CI, 0.72–0.98).[165]

Results from subsequent meta-analyses and observational studies have supported the suggested efficacy of pioglitazone in persons with ASCVD.[166–169] Notably, the magnitude of the estimated treatment benefit with pioglitazone across these studies aligns with contemporary meta-analyses estimates of the effects of SGLT2 inhibitors and GLP-1 RAs on the same composite MACE outcome.[155,164]

TZDs enhance fluid retention and the risk of peripheral oedema, especially with concomitant insulin use and in the context of kidney dysfunction. In addition, TZDs increase the risk of HF, with the incremental risk of HF with pioglitazone at an estimated 0.4% annualized, absolute increase.[170] HF associated with TZDs appears to be attributable to expanded plasma volume, with no evidence of myocardial toxicity.[171] TZDs induce weight gain due to adipose tissue expansion, but with weight redistributed predominantly to less metabolically active adipose tissue; weight gain may be the greatest concern of patients and clinicians with the TZD class. Based on the data and net benefit-risk assessment, it is reasonable to consider using pioglitazone to mitigate ASCVD risk in patients with T2DM and prevalent ASCVD.

5.3.2. Glucose-lowering medications with cardiovascular safety but not incremental efficacy demonstrated in dedicated cardiovascular outcomes trials

5.3.2.1. Dipeptidyl peptidase-4 inhibitors

Five randomized CV safety trials in populations with T2DM with or at high risk of ASCVD have assessed the CV effects of dipeptidyl peptidase-4 (DPP-4) inhibitors (Supplementary data online, *Table S9*): saxagliptin, alogliptin, sitagliptin, and linagliptin each vs. placebo, and linagliptin vs. glimepiride.[172–175] All four of the placebo-controlled trials demonstrated statistical non-inferiority but not superiority for the DPP-4 inhibitors in the primary MACE endpoint. In the SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus—Thrombolysis in Myocardial Infarction 53) trial, saxagliptin statistically significantly increased the risk of hospitalization for HF vs. placebo.[176] Numerically, more HF events occurred with alogliptin vs. placebo in the EXAMINE (Cardiovascular Outcomes Study of Alogliptin in Patients With Type 2 Diabetes and Acute Coronary Syndrome) trial, though this difference was not nominally significant.[177]

These observations led to the development and regulatory filing of prospective HF analysis plans for the TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) and CARMELINA (Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus) trials, each of which revealed no increased risk of HF with either sitagliptin or linagliptin compared with placebo.[178,179] In the CAROLINA (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes) trial, linagliptin was compared with the active comparator glimepiride, demonstrating no difference in any assessed CV or kidney outcome, though noting a higher risk of hypoglycaemia with glimepiride.[180]

5.3.2.2. Lixisenatide and exenatide

Of the eight GLP-1 RAs evaluated in CVOTs, two have demonstrated safety but not incremental efficacy. In the ELIXA trial, lixisenatide 10 or 20 μg o.d. was non-inferior to placebo, but did not significantly affect a four-point MACE (three-point MACE plus hospitalization for unstable angina) in patients with T2DM post-ACS.[158] In the EXSCEL trial of patients with T2DM in whom 73% had experienced a previous CV event, exenatide extended-release 2 mg once weekly showed non-inferiority but not superiority to placebo for the primary outcome of CV death, MI, and stroke.[159]

5.3.2.3. Insulin

Two basal insulins have been formally evaluated in dedicated CVOTs. In the ORIGIN (Outcome Reduction With Initial Glargine Intervention) trial, 12 537 patients (mean age 63.5 years) at high CVD risk with impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or T2DM were randomized to insulin glargine titrated to a fasting blood glucose level of ≤5.3 mmol/L (≤95 mg/dL) or standard care.[86] After a median follow-up of 6.2 years, the incidence of CV outcomes did not differ between the two groups.

The DEVOTE (A Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Subjects With Type 2 Diabetes at High Risk of Cardiovascular Events) trial, a randomized, double-blind comparison of the ultra-long-acting, o.d. insulin degludec vs. insulin glargine U100, enrolled 7637 patients with T2DM with ASCVD or at high CV risk.[181] Over a median follow-up of 1.8 years, there was no significant difference in the primary composite of CV death, non-fatal MI, or non-fatal stroke between groups. A significantly lower frequency of hypoglycaemia was observed in the degludec arm compared with the glargine arm.[181]

5.3.2.4. Glimepiride

Based on the findings of statistical non-inferiority of linagliptin vs. placebo in CARMELINA coupled with the non-inferiority of linagliptin vs. glimepiride demonstrated in CAROLINA, one might conclude that glimepiride is most likely not different from placebo with regards to CV safety.[180] Thus, the long-lasting uncertainty about the CV safety of sulphonylureas may no longer be clinically relevant for glimeperide, at least in patients with a shorter duration of diabetes like those enrolled in the CAROLINA trial (median duration of T2DM ~6 years).[182]

5.3.3. Cardiovascular considerations of older glucose-lowering medications not tested in dedicated cardiovascular outcomes trials

5.3.3.1. Metformin

Despite its long history as the recommended first-line treatment of hyperglycaemia for patients with T2DM, there have been no dedicated randomized trials to rigorously assess the CV safety or efficacy of metformin. Randomized trials that have reported CV outcomes with metformin are most-commonly limited by small sample sizes and few CV events for analysis, yielding low statistical power and substantially uncertain statistical precision of the estimates.

The largest randomized trial with the most encouraging CV results for metformin was a nested randomized trial of 753 patients in the UKPDS who were overweight or obese at trial entry, comparing conventional glucose targets with a policy of intensive glucose lowering with metformin.[183] In overweight and obese patients with newly diagnosed T2DM without previous CVD, metformin reduced MI by 39%, coronary death by 50%, and stroke by 41% over a median period of 10.7 years. However, with only 39 MIs and 16 coronary deaths in the metformin arm of the UKPDS, the precision of these efficacy estimates is largely uncertain. Initial randomization to metformin in the UKPDS was also associated with a lower incidence of MI and longer survival during an additional 8–10 years of passive follow-up.[132]

In meta-analyses of 13 randomized clinical trials evaluating the CV effects of metformin vs. placebo or active control, including the data from the UKPDS, none of the differences in assessed CV outcomes was statistically significant.[184] The pooled HRs (95% CIs) were: all-cause mortality 0.96 (0.84–1.09); CV death 0.97 (0.80–1.16); MI 0.89 (0.75–1.06); stroke 1.04 (0.73–1.48); and peripheral vascular disease 0.81 (0.50–1.31). While failing to demonstrate CV efficacy, the upper confidence limits of each of the outcomes analysed provide reassurance on the CV safety of metformin.

Given the inconclusive results regarding the CV effects of metformin outlined above, metformin should not be a prerequisite for considering SGLT2 inhibitor or GLP-1 RA treatment for CV benefits. However, most patients in CVOTs with SGLT2 inhibitors or GLP-1 RAs were treated with metformin. Therefore, in patients already prescribed metformin, SGLT2 inhibitors and/or GLP-1 RAs should be added, independent of the need for additional glucose control. In patients with T2DM and ASCVD not treated with metformin, an SGLT2 inhibitor and/or GLP-1 RA should be given first line, and metformin should be considered for those who thereafter warrant additional glucose control. This Class IIa recommendation for metformin is based on the weight of opinion rather than the weight of evidence; results from meta-analyses of observational studies suggest associations with better CV outcome, but this is not supported by results from meta-analyses restricted to randomized trials in patients with T2DM and ASCVD, where no statistically significant effect of metformin has been observed for any major CV outcome.[184,185]

In patients without ASCVD or severe TOD at low or moderate CV risk, treatment with metformin should be considered based on the metformin data from the randomized sub-group with overweight or obesity from the UKPDS.[183] For patients without ASCVD or severe TOD at high or very CV high risk, treatment with metformin may be considered based on expert consensus of the Task Force.

5.3.3.2. Sulphonylureas

Excepting glimepiride, which was assessed for CV safety and efficacy head-to-head against linagliptin in the CAROLINA trial, and gliclazide-modified release, which was compared with usual care (that could have included treatment with a sulphonylurea other than gliclazide) in the ADVANCE trial, dedicated CV safety assessments have not been conducted for the other sulphonylureas.[132,173,174,184] In the UKPDS, which enrolled patients with newly diagnosed T2DM, the sulphonylureas chlorpropamide and glibenclamide (also known as glyburide) did not have statistically significant effects on CV outcomes, but importantly, no concerning signal of CV risk was observed.[127] Likewise, in the ADVANCE trial evaluating more intensive glucose control vs. usual targets, patients randomized to the more intensive arm were randomized to treatment with gliclazide-modified release.[128] While the gliclazide-based more intensive control strategy did not significantly improve CV outcomes, there were no major CV safety concerns observed. The relative CV safety of gliclazide and glimepiride is somewhat supported by results of contemporary real-world data analyses.[186]

5.3.4. Special considerations

5.3.4.1. Hypoglycaemia and cardiovascular risk

Results from numerous studies have demonstrated associations between hypoglycaemia and CV events, with substantial uncertainty about whether these relationships are causal or simply associations. Results from randomized trials challenge a causal relationship between hypoglycaemia and adverse CV outcomes. For example, insulin degludec compared with glargine in the DEVOTE trial reduced the risk of hypoglycaemia, yet this did not translate into any difference in CV risk.[181] Likewise, in the CAROLINA randomized trial, while glimepiride was associated with significantly more hypoglycaemia than the DPP-4 inhibitor linagliptin, MACE did not differ between the two randomized groups.[180] The results of these two trials challenge, to some degree, the premise that avoiding hypoglycaemia may improve CV risk. In analyses of data from the TECOS randomized trial, which compared sitagliptin with placebo, hypoglycaemia events were independently associated with subsequent CV events, but importantly, the converse was also true.[139] A non-fatal CV event was independently associated with subsequent hypoglycaemia. Similar results were confirmed in other trials.[140,187,188]

Therefore, the data suggest that the relationship between hypoglycaemia events and risk of CV events (and vice versa) is most likely one of association rather than causation, each risk marking vulnerability and frailty of high CV risk patients. Still, in certain patients, hypoglycaemia may directly contribute to CV risk. In addition, avoiding hypoglycaemia remains important given the unpleasant patient experience and, for severe events, life-threatening nature if third-party assistance is not available.

5.3.4.2. Effects on weight

The choice of glucose-lowering therapy is often influenced by effects on weight, when weight loss or avoiding weight gain is a priority. The insulins, sulphonylureas, and pioglitazone all cause weight gain; metformin, acarbose, and the DPP-4 inhibitors are weight neutral or may result in small amounts of weight loss; and the SGLT2 inhibitors and GLP-1 RAs are associated with clinically meaningful weight loss, with weight effects of GLP-1 RAs being more pronounced than that of SGLT2 inhibitors.

5.3.5. Implications of results from cardiovascular outcomes trials of glucose-lowering medications

Beginning with the EMPA-REG OUTCOME trial results in 2015, an ever-increasing body of evidence has accumulated from many CVOTs of glucose-lowering medications for patients with T2DM that indicate CV benefits from using selected SGLT2 inhibitors and GLP-1 RAs in patients with ASCVD. The combined results obtained from CVOTs using GLP-1 RAs and SGLT2 inhibitors support the primacy of their recommendation for all patients with T2DM with prevalent ASCVD, with such considerations made independently of decisions about glycaemic management (*Figures 7 and 8*). Just as T2DM informs prescription of statins, antithrombotic therapy, angiotensin-converting enzyme inhibitors (ACE-Is)/angiotensin-II receptor blockers (ARBs), and other CV risk-mitigating therapies independent of glycaemic considerations, the same should now apply to prescribing SGLT2 inhibitors and/or GLP-1 RAs.

The mechanisms of CV benefits of the novel glucose-lowering medications with proven efficacy remain incompletely understood. For the GLP-1 RAs, CV efficacy is driven by reduced risk of

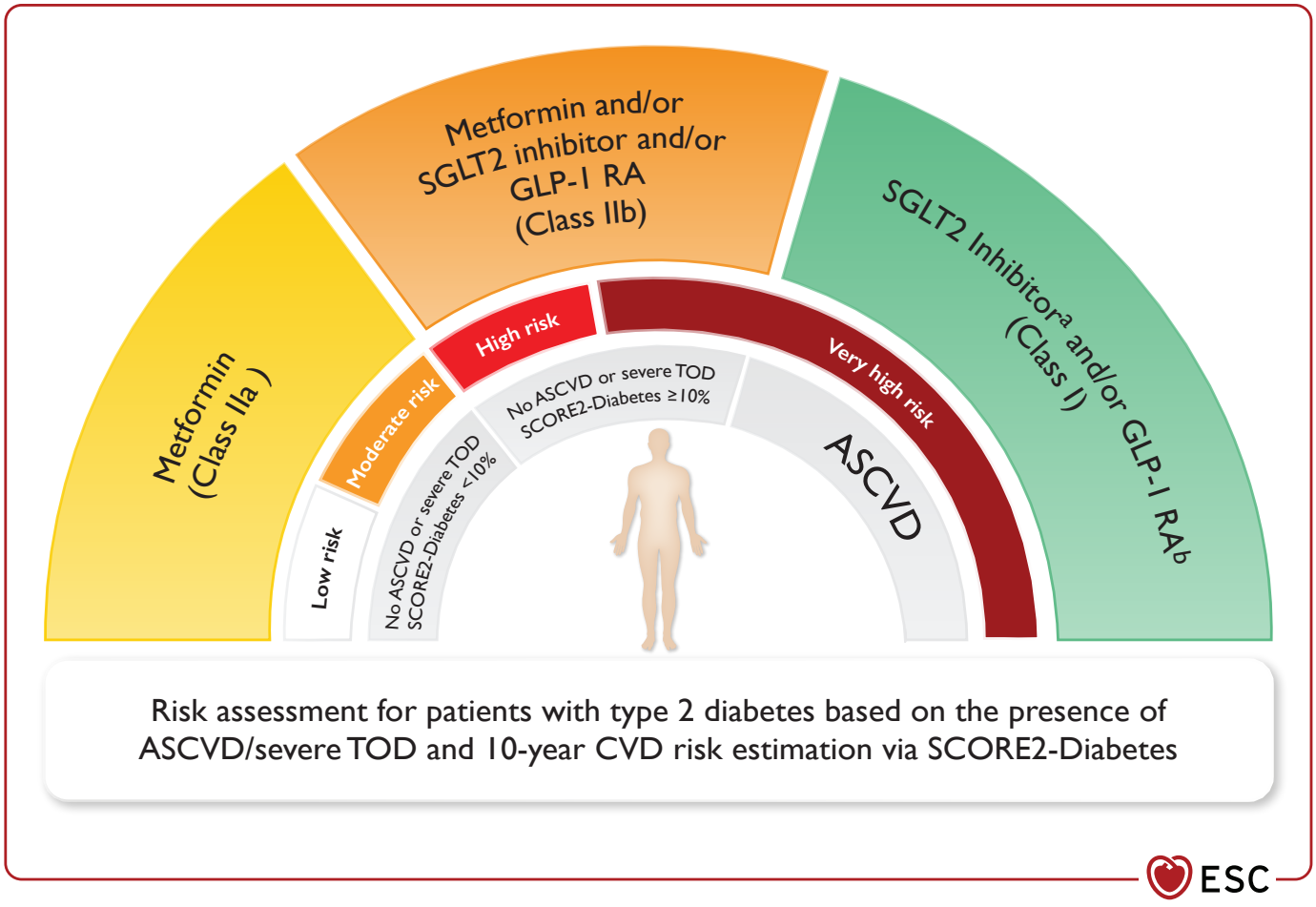

Figure 7 Glucose-lowering treatment for patients with type 2 diabetes to reduce cardiovascular risk based on the presence of atherosclerotic cardiovascular disease/severe target-organ damage and 10-year cardiovascular disease risk estimation via SCORE2-Diabetes. ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; s.c., subcutaneous; SGLT2, sodium–glucose co-transporter-2; T2DM, type 2 diabetes mellitus; TOD, target-organ damage. Risk categorization is based on the presence of ASCVD/severe TOD and 10-year CVD risk estimation via SCORE2-Diabetes. For patients with ASCVD, only the Class I recommendation is shown. Treatment recommendations for patients with T2DM and severe TOD are described in *Section 9*. Severe TOD defined as eGFR <45 mL/min/1.73 m^2 irrespective of albuminuria; or eGFR 45–59 mL/min/1.73 m^2 and microalbuminuria (UACR 30–300 mg/g; stage A2); or proteinuria (UACR >300 mg/g; stage A3); or presence of microvascular disease in at least three different sites [e.g. microalbuminuria (stage A2) plus retinopathy plus neuropathy]. [a]SGLT2 inhibitors with proven CV benefit: empagliflozin, canagliflozin, dapagliflozin, sotagliflozin. [b]GLP-1 RAs with proven CV benefit: liraglutide, semaglutide s.c., dulaglutide, efpeglenatide.

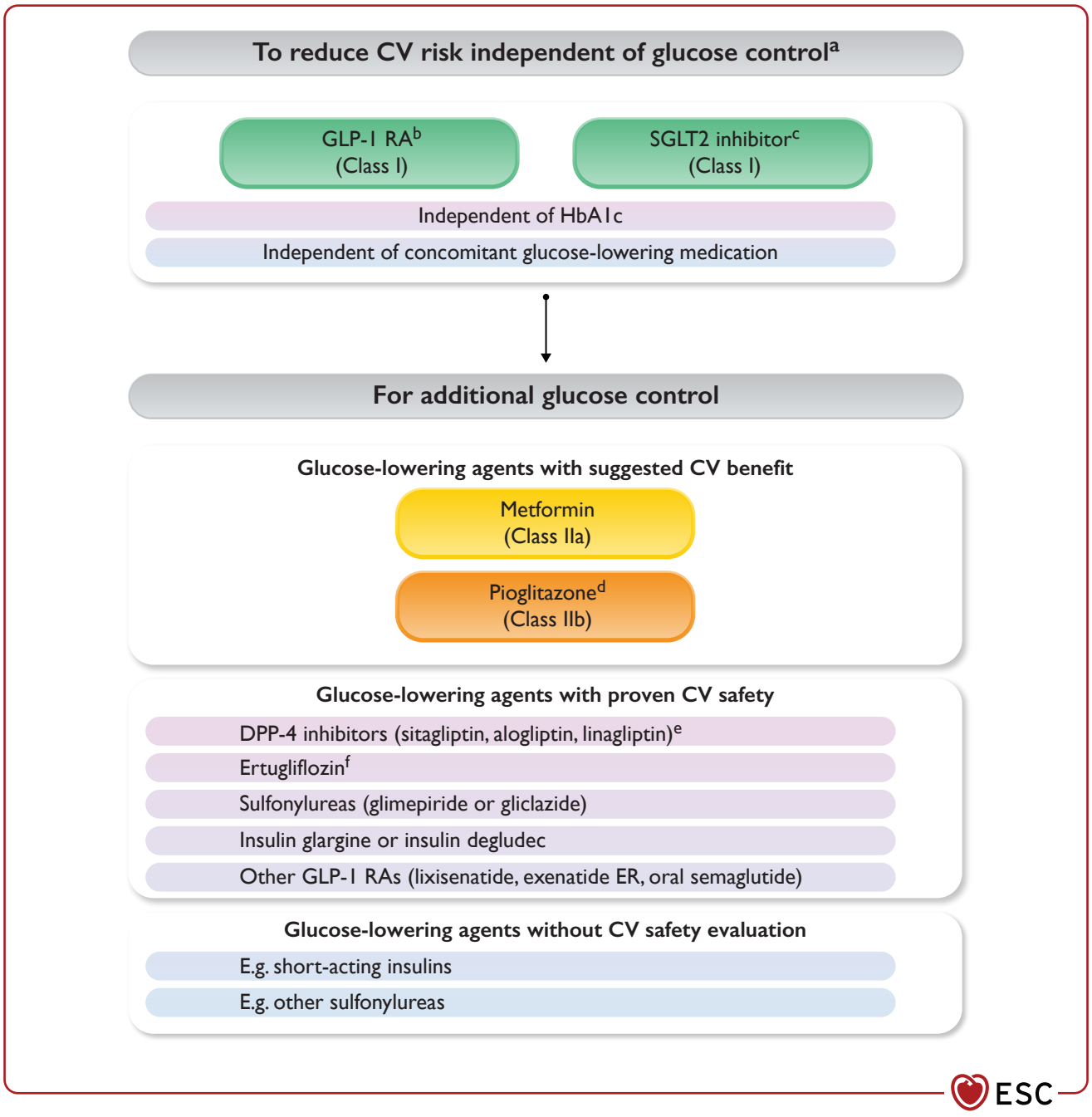

Figure 8 Glucose-lowering treatment for patients with type 2 diabetes and atherosclerotic cardiovascular disease to reduce cardiovascular risk. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; ER, extended release; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; MACE, major adverse cardiovascular events; s.c., subcutaneous; SGLT2, sodium–glucose co-transporter-2; T2DM, type 2 diabetes mellitus. [a]In patients with ASCVD and T2DM, it is recommended to treat with a GLP-1 RA and/or SGLT2 inhibitor with proven benefit to reduce CV risk, independent of HbA1c and concomitant glucose-lowering medications. If additional glucose control is needed, treatment with metformin should be considered and treatment with pioglitazone may be considered. [b]GLP-1 RAs with proven CV benefit: liraglutide, semaglutide s.c., dulaglutide, efpeglenatide. [c]SGLT2 inhibitors with proven CV benefit: empagliflozin, canagliflozin, dapagliflozin, sotagliflozin. [d]Pioglitazone should not be used in patients with heart failure; the use in CKD requires caution as intravascular volume expansion and heart failure are common at reduced eGFR. [e]DPP-4 inhibitors should not be used in patients on GLP-1 RAs. [f]Ertugliflozin in the VERTIS CV trial showed safety with respect to three-point MACE but no benefit.

Recommendation Table 8 — Recommendations for glucose-lowering treatment for patients with type 2 diabetes and atherosclerotic cardiovascular disease to reduce cardiovascular risk

Recommendations	Class[a]	Level[b]
It is recommended to prioritize the use of glucose-lowering agents with proven CV benefits[c,d] followed by agents with proven CV safety[e] over agents without proven CV benefit or proven CV safety.	I	C
Sodium–glucose co-transporter-2 inhibitors		
SGLT2 inhibitors with proven CV benefit[c] are recommended in patients with T2DM and ASCVD to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.[71,150–152,155,189]	I	A
Glucagon-like peptide-1 receptor agonists		
GLP-1 RAs with proven CV benefit[d] are recommended in patients with T2DM and ASCVD to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.[70,72,161,163,164]	I	A
Other glucose-lowering medications to reduce cardiovascular risk		
If additional glucose control is needed, metformin should be considered in patients with T2DM and ASCVD.	IIa	C
If additional glucose control is needed, pioglitazone may be considered in patients with T2DM and ASCVD without HF.[165]	IIb	B
In patients with T2DM without ASCVD or severe TOD[c] at high or very high risk, treatment with metformin may be considered to reduce CV risk.	IIb	C
In patients with T2DM without ASCVD or severe TOD[c] but with a calculated 10-year CVD risk[d] ≥10%, treatment with a SGLT2 inhibitor or GLP-1 RA may be considered to reduce CV risk.[155,164]	IIb	C

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; HF, heart failure; s.c., subcutaneous; SGLT2, sodium–glucose co-transporter-2; T2DM, type 2 diabetes mellitus; TOD, target-organ damage; UACR, urinary albumin-to-creatinine ratio.
[a]Class of recommendation.
[b]Level of evidence.
[c]Empagliflozin, canagliflozin, dapagliflozin, sotagliflozin.
[d]Liraglutide, semaglutide s.c., dulaglutide, efpeglenatide.
[e]Metformin, pioglitazone, DPP-4 inhibitor (sitagliptin, alogliptin, linagliptin), glimepiride, gliclazide, insulin glargine, insulin degludec, ertugliflozin, lixisenatide, exenatide (extended release), oral semaglutide.

Recommendation Table 9 — Recommendation for glucose-lowering treatment for patients with type 2 diabetes without atherosclerotic cardiovascular disease or severe target-organ damage to reduce cardiovascular risk

Recommendations	Class[a]	Level[b]
In patients with T2DM without ASCVD or severe TOD[c] at low or moderate risk, treatment with metformin should be considered to reduce CV risk.[183]	IIa	C

Continued

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium–glucose co-transporter-2; T2DM, type 2 diabetes mellitus; TOD, target-organ damage; UACR, urinary albumin-to-creatinine ratio.
[a]Class of recommendation.
[b]Level of evidence.
[c]Severe TOD defined as eGFR <45 mL/min/1.73 m^2 irrespective of albuminuria; or eGFR 45–59 mL/min/1.73 m^2 and microalbuminuria (UACR 30–300 mg/g; stage A2); or proteinuria (UACR >300 mg/g; stage A3); or presence of microvascular disease in at least three different sites [e.g. microalbuminuria (stage A2) plus retinopathy plus neuropathy].
[d]Using SCORE2-Diabetes.

ASCVD-related events.[164] While empagliflozin and canagliflozin improved the composite of CV death, MI, and stroke, all of the SGLT2 inhibitors reduce HF-related endpoints (*Section 7*) and progression of kidney disease (*Section 9*).[155,190] Thus, SGLT2 inhibitors are recommended to reduce HF hospitalization in patients with T2DM with or at risk of HF, or who have CKD. In patients with newly diagnosed T2DM without CVD or other major CV risk factors who are at low or moderate CV risk, factors other than mitigating CV and kidney risk may play a greater role in selecting glucose-lowering medications, such as affordability, accessibility, side effects, weight benefits, tolerability, and ease of use.

5.4. Blood pressure and diabetes

In the most recent ESC/EURObservational Research Programme (EORP) EUROASPIRE surveys, history of hypertension was present in 80% of men and 87% of women with known diabetes and in 74% of men and 81% of women with newly diagnosed diabetes with a history of coronary heart disease (CHD).[191]

5.4.1. Screening and diagnosis

Regular BP measurements under standardized conditions are mandatory in all patients with diabetes (*Figure 9*; *Table 8*). Hypertension should be confirmed in both arms using multiple readings, including measurements on separate days.[48,157] In patients with CVD and values >180/110 mmHg, it could be reasonable to diagnose hypertension at a single visit.[192] Details on BP measurements are comprehensively summarized in the 2018 ESC/European Society of Hypertension (ESH) Guidelines for the management of arterial hypertension and in the Supplementary data online, *Section 2.6.1*.[193]

5.4.2. Treatment targets

Randomized controlled trials have shown the benefit (reduction of stroke, coronary events, and kidney disease) of lowering SBP to

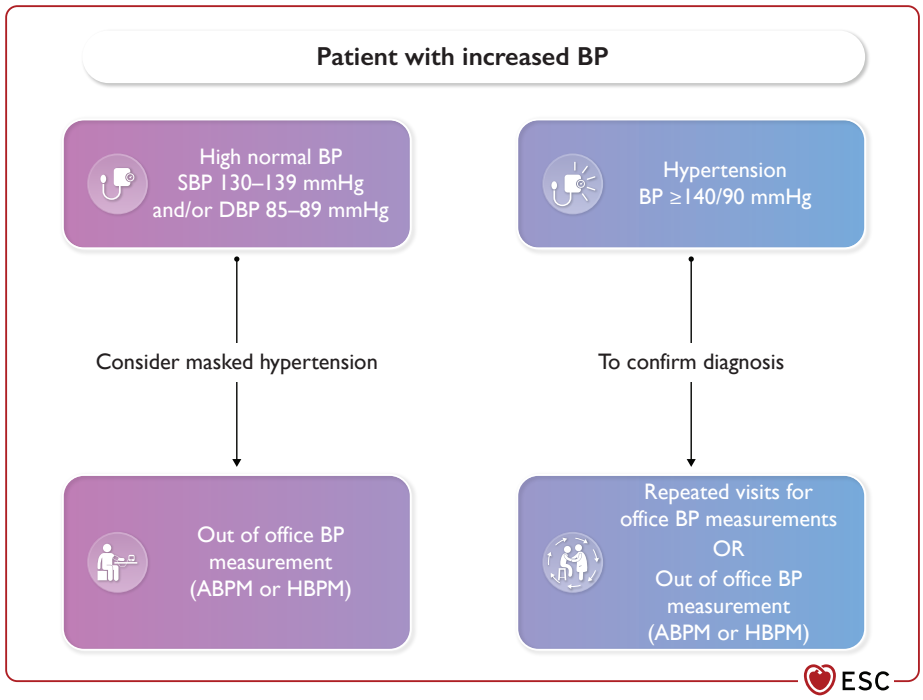

Figure 9 Screening and diagnosis of hypertension in patients with diabetes. ABPM, ambulatory blood pressure monitoring; BP, blood pressure; DBP, diastolic blood pressure; HBPM, home blood pressure monitoring; SBP, systolic blood pressure. Figure adapted from Williams *et al.* 2018.[193]

Table 8 Blood pressure measurement

BP measurements at the initial and every follow-up visit (at every routine clinical visit).
Patients should be seated comfortably in a quiet environment for 5 min before beginning BP measurements. Three BP measurements should be recorded, 1–2 min apart, and additional measurements if the first two readings differ by >10 mmHg. BP is recorded as the average of the last two BP readings.
Measure BP 1 min and 3 min after standing from a seated position in all patients on initial visit to exclude orthostatic hypotension; lying and standing BP measurements should also be considered in subsequent visits.
Out-of-office BP measurement with ambulatory and/or home BP monitoring should be implemented when feasible. Masked hypertension should be considered in patients with normal and high-normal office BP but with HMOD or at high cardiovascular risk.[193]

BP, blood pressure; HMOD, hypertension-mediated organ damage.

<140 mmHg and diastolic blood pressure (DBP) to <90 mmHg in patients with diabetes. However, the optimal BP target in patients with diabetes is still a matter of debate. The UKPDS post-trial, 10-year follow-up study reported no benefits persisting from the earlier period of tight BP control with respect to macrovascular events, death, and microvascular complications, while initial between-group BP differences were no longer maintained.[132] RCTs evaluating the benefits and risks of more intense compared with standard hypertension treatment strategies in patients with diabetes are summarized in Supplementary data online, *Table S10*.

In a meta-analysis of RCTs involving patients with diabetes or prediabetes, an SBP reduction to ≤135 mmHg compared with a less intensive control reduced the RR of all-cause mortality by 10% (odds ratio [OR] 0.90; 95% CI, 0.83–0.98), whereas more intensive BP control (≤130 mmHg) was associated with a greater reduction in stroke but did not reduce other events.[194,195] Similarly, anti-hypertensive treatment significantly reduced mortality in people with T2DM, CAD, HF, and stroke, with an achieved mean SBP of 138 mmHg, whereas only stroke was reduced significantly, with a mean SBP of 122 mmHg compared with higher BP values.[196] Thus, reducing SBP to <130 mmHg may benefit patients with a particularly high risk of a cerebrovascular event, such as those with a history of stroke.[193,194,196–200] However, SBP >140 mmHg or <120 mmHg were related to higher risk of adverse renal outcomes in patients with diabetes when compared with those without diabetes and with high CV risk.[199–202]

The 2018 ESC/ESH Guidelines for the management of arterial hypertension recommend that in all patients with diabetes, office BP should be targeted to an SBP of 130 mmHg, and lower if tolerated but not <120 mmHg; DBP should be lowered to <80 mmHg but not <70 mmHg.[193] In older patients (age ≥65 years), the SBP target range should be 130–140 mmHg if tolerated.[193] However, more recent data challenge these recommendations for all patients with diabetes, and highlight a potential need for more individualized target levels.[157,203,204]

The 2021 ESC Prevention Guideline recommends office SBP treatment target ranges of 120–130 mmHg in patients with diabetes, with lower SBP acceptable if tolerated until the age of 69 years.[48] In patients aged ≥70 years, SBP values <140 mmHg, down to 130 mmHg if tolerated are recommended. DBP treatment target <80 mmHg is recommended for all treated patients.

5.4.3. Management of hypertension

5.4.3.1. Effects of lifestyle intervention and weight loss

Diets rich in vegetables, fruits, and low-fat dairy products, such as the Mediterranean diets and Dietary Approaches to Stop Hypertension-style eating patterns (including reducing sodium to <100 mmol/day and increasing potassium intake), improve BP control.[205–207]

Long-term exercise training intervention modestly but significantly reduces SBP (by −7 mmHg) and DBP (by −5 mmHg). Ideally, an exercise prescription aimed at lowering BP in individuals with normal BP or hypertension would include a mix of predominantly aerobic exercise training supplemented with dynamic resistance exercise training.[208]

A marked improvement in CV risk factors (hypertension, dyslipidaemia, diabetes), associated with marked weight loss, was observed after bariatric surgery.[209] In the Look AHEAD trial, those who lost 5 to <10% of body weight had increased odds of achieving a 5 mmHg decrease in SBP and DBP compared with those who lost >10% or <5%.[210] The frequency of CV complications appears to be modulated by ethnicity or racial identity.[193,211,212]

5.4.3.2. Pharmacological treatments in patients with diabetes

If office SBP is ≥140 mmHg and/or DBP is ≥90 mmHg, drug therapy is necessary in combination with non-pharmacological treatment. It is recommended to start with a combination therapy.[48] All available BP-lowering drugs can be used, but evidence strongly supports using a renin–angiotensin system (RAS) inhibitor (ACE-I, ARB), particularly in patients with evidence of end-organ damage (albuminuria and left ventricular [LV] hypertrophy).[213–216] However, in a recent meta-analysis, RAS inhibitors were not superior to other classes of anti-hypertensive drugs for reducing total or CV mortality and renal events.[217]

Controlling BP often requires multiple drug therapy with an RAS inhibitor and a calcium channel blocker (CCB) or diuretic, while the combination of an ACE-I with an ARB is not recommended.[218] Consider beta-blockers at any treatment step when specifically indicated, e.g. HF, angina, post-MI, AF, or younger women with or planning pregnancy.[193] A combination of two or more drugs at fixed doses in a single pill should be considered to improve adherence and to achieve earlier control of BP.[48,219]

In apparent resistant (including MRA-resistant) hypertension in patients with HFpEF (61% diabetes; *post-hoc* analysis of PARAGON-HF [Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction] trial) sacubitril/valsartan helped to better control BP compared with valsartan.[220]

5.4.3.3. Blood pressure changes with glucose-lowering agents

Trials testing GLP-1 RAs have shown a BP decrease with these drugs, partly due to weight loss. A sustained decrease in BP was observed with semaglutide therapy (SBP dose dependent: −1.3 to −2.6 mmHg) with a slight increase in heart rate (+2 to 2.5 beats per minute [b.p.m.]).[72] Similar effects were seen in other studies of GLP-1 RAs and derived from meta-analysis.[161,221,222]

SGLT2 inhibitors induced a larger BP decrease than did GLP-1 RAs without changing heart rate.[223–225] A recent meta-analysis including seven RCTs demonstrated that SGLT2 inhibitors were associated with an average reduction of 3.6/1.7 mmHg (systolic/diastolic) in 24 h ambulatory BP, which is comparable with efficacy of low-dose hydrochlorothiazide.[224–226]

5.4.4. Sex-specific aspects

In general, the diagnosis and treatment of hypertension is comparable between sexes, except for women of child-bearing potential or during pregnancy, when some drugs, such as RAS blockers, can have adverse effects on the foetus, especially in early gestation.[227] The possible effect of oral contraceptives on BP should also be considered.[48] There is some evidence from RCTs that BP targets during pregnancy should range from 110 to 135 mmHg for SBP and 80 to 85 mmHg for DBP.[228] This is also supported by the recent CHAP (Chronic Hypertension and Pregnancy) study of mild chronic hypertension in pregnancy, where 16% of the pregnant women had diabetes.[229] The strategy targeting a BP of <140/90 mmHg was related with better pregnancy outcomes without an increase in the number of Small for Gestational Age babies.

Women usually show greater differences in BP and higher proportions of hypertension than men already at diagnosis of T2DM compared with women and men without T2DM, and worse BP control thereafter.[191,230] Moreover sex-specific, hypertension-mediated organ damage was evidenced with a very high risk of HFpEF in women, especially in the presence of diabetes.[231]

Recommendation Table 10 — Recommendations for blood pressure management in patients with diabetes

Recommendations	Class[a]	Level[b]
Screening for hypertension		
Regular BP measurements[c] are recommended in all patients with diabetes to detect and treat hypertension to reduce CV risk.[193,232,233]	I	A
Treatment targets		
Anti-hypertensive drug treatment is recommended for people with diabetes when office BP is ≥140/90 mmHg.[196,202,234,235]	I	A
It is recommended to treat hypertension in patients with diabetes in an individualized manner. The BP goal is to target SBP to 130 mmHg and <130 mmHg if tolerated, but not <120 mmHg. In older people (age >65 years), it is recommended to target SBP to 130–139 mmHg.[196,236–238]	I	A
An on-treatment SBP target of <130 mmHg may be considered in patients with diabetes at particularly high risk of a cerebrovascular event to further reduce their risk of stroke.[194–198,239,240]	IIb	B
Treatment and evaluation		
Lifestyle changes (weight loss if overweight, physical activity, alcohol restriction, sodium restriction, increased consumption of vegetables, using low-fat dairy products) are recommended in patients with diabetes and hypertension.[205–207,210]	I	A
It is recommended to initiate treatment with a combination of a RAS inhibitor and a CCB or thiazide/thiazide-like diuretic.[196,213–216,218,241]	I	A
Home BP self-monitoring should be considered in patients with diabetes on anti-hypertensive treatments to check that BP is appropriately controlled.[242]	IIa	B
24 h ambulatory blood pressure monitoring should be considered to assess abnormal 24 h BP patterns, including nocturnal hypertension and reduced or reversed nocturnal BP dipping, and to adjust anti-hypertensive treatment.[243]	IIa	B

BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; RAS, renin–angiotensin system; SBP, systolic blood pressure.
[a]Class of recommendation.
[b]Level of evidence.
[c]Ideally at every encounter.

5.5. Lipids and diabetes

A cluster of lipid and apolipoprotein abnormalities accompanies diabetes. The core components are moderately elevated plasma triglyceride (TG), TG-rich lipoprotein (TRL), and TRL cholesterol levels, normal-to-mildly elevated low-density lipoprotein-cholesterol (LDL-C), and low high-density lipoprotein-cholesterol (HDL-C). Other features comprise structure and function of lipoproteins, e.g. small dense LDL and HDL particles. The same abnormalities are also reported in patients with T1DM, whose long-lasting exposure to dyslipidaemia might induce atherosclerosis as early as in adolescence. In T1DM, high LDL-C values are seen in patients with uncontrolled glycaemia, while high levels of HDL-C might be pro-inflammatory and therefore atherogenic instead of protective.[244] In well-controlled T1DM, HDL-C levels tend to be normal (or even slightly elevated), as are serum TGs.[245]

5.5.1. Treatment targets

Epidemiological studies have shown that high levels of LDL-C and non-HDL-C and low levels of HDL-C are associated with an increased risk of CV events and mortality in patients with and without diabetes.[246] Conversely, RCTs with lipid-lowering agents in patients at risk of CV events (including patients with T2DM) have demonstrated a log-linear proportional reduction of CV events and mortality for each 1 mmol reduction of LDL-C.[247] LDL-C is the primary target of lipid-lowering therapies. A secondary goal of non-HDL-C should also be considered in patients with diabetes and combined dyslipidaemias, although there are limited data from interventional trials. Treatment targets differ among patients with diabetes based on their CV risk (Section 4; *Figure 10*).[48] Due to the lack of evidence, no clear recommendations can be given for patients with T2DM at low CV risk.

5.5.2. Lipid-lowering agents

5.5.2.1. Statins

Statins remain the first-line therapy to reduce LDL-C levels in patients with diabetes and dyslipidaemia, due to their efficacy in preventing CV events and reducing CV mortality with no evidence for sex differences.[248,249]

High-intensity statins (rosuvastatin and atorvastatin) are indicated in patients with diabetes at high or very high CV risk, as they lower LDL-C by 40–63% and significantly reduce the incidence of major cerebral and coronary complications.[250] This beneficial effect outweighs the potential diabetogenic effect of these drugs, estimated as a 9% increased risk of incident diabetes, especially in older patients and in patients already at risk of developing diabetes.[251,252] Similar benefits were seen in both T1DM and T2DM.[253–255]

Statins are safe and generally well tolerated. Subjective adverse events (such as fatigue, myalgias, and nervous system symptoms) are more frequent than objective adverse events due to the nocebo effect, with women experiencing adverse events more frequently than men.[256] In most cases of myopathy or rhabdomyolysis, there are drug interactions with a higher-than-standard dose of statin or combination with gemfibrozil.[200] Evidence indicates that 70–90% of patients who report statin intolerance are able to take a statin when re-challenged.[257]

5.5.2.2. Ezetimibe

Lowering of LDL-C can be further intensified by adding ezetimibe to a statin, which reduces cholesterol absorption from the ileum.[258] The IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) trial showed significantly reduced MACE (composite of CV death, non-fatal MI, unstable angina requiring re-hospitalization, coronary revascularization ≥30 days after

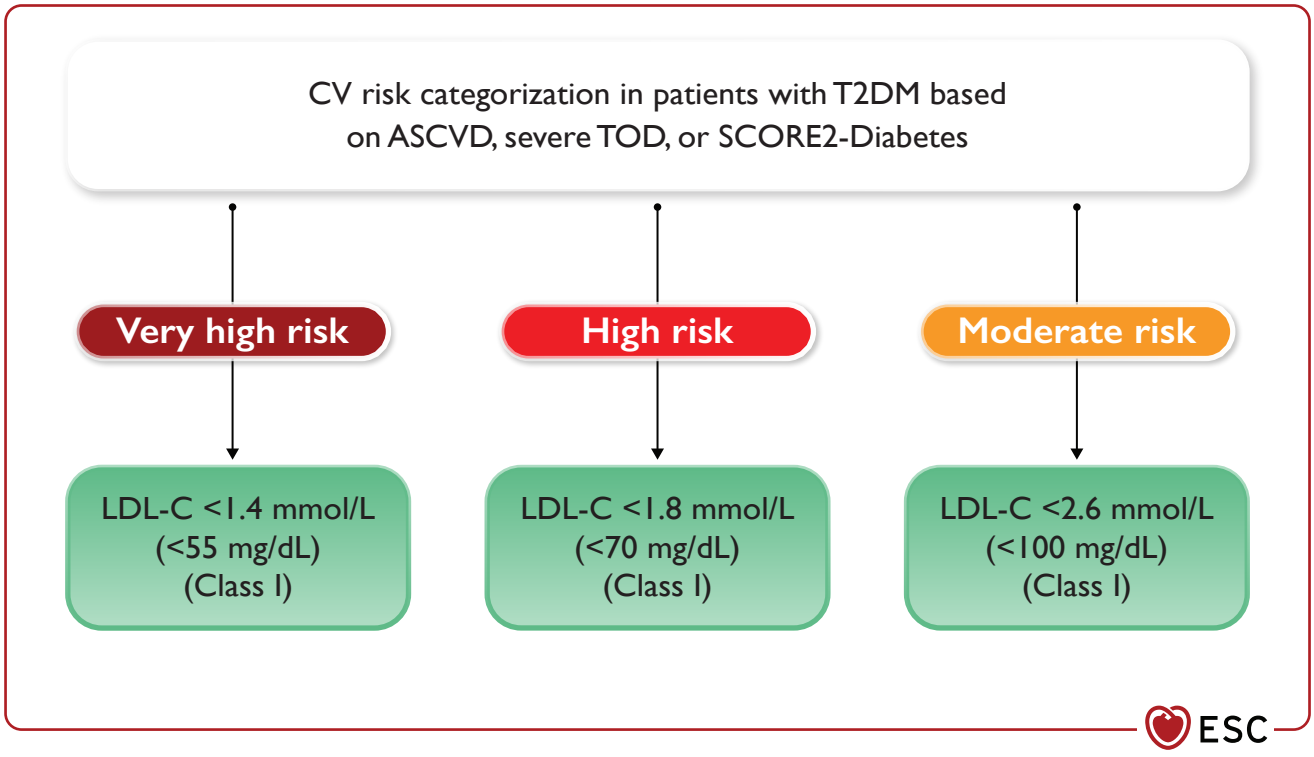

Figure 10 Recommended low-density lipoprotein-cholesterol targets by cardiovascular risk categories in patients with type 2 diabetes. ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; LDL-C, low-density lipoprotein-cholesterol; TOD, target-organ damage; T2DM, type 2 diabetes mellitus.

randomization, or non-fatal stroke; HR 0.94; 95% CI, 0.89–0.99) in patients post-ACS receiving simvastatin plus ezetimibe, with a stronger benefit in the sub-group of patients with diabetes (HR 0.85; 95% CI, 0.78–0.94; P <0.001).[259,260] The combination of ezetimibe with a statin is therefore recommended in patients with diabetes and a recent ACS, especially when an LDL-C target <1.4 mmol/L (55 mg/dL) is required and not achieved with a statin alone. Young adults with T1DM have increased cholesterol absorption, as shown in a recent study, suggesting greater efficacy of ezetimibe in this population, which remains to be assessed with dedicated RCTs.[261]

5.5.2.3. Proprotein convertase subtilisin/kexin type 9 inhibitors

The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors evolocumab and alirocumab are monoclonal antibodies that strongly reduce plasma LDL-C, targeting the protein involved in regulating the LDL receptor on the hepatocyte.[262] Administered alongside high-intensity statin therapy (with or without ezetimibe), PCSK9 inhibitors significantly reduced MACE in the sub-groups of patients with diabetes with ASCVD enrolled in the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial and in the ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial, respectively.[263,264] In particular, evolocumab showed a 17% RR reduction of a composite primary endpoint of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization in patients with diabetes included in the FOURIER trial (HR 0.83; 95% CI, 0.75–0.93; $P = 0.0008$).[263] Compared with placebo, evolocumab also significantly reduced other atherogenic lipids (i.e. TGs, non-HDL-C, apolipoprotein B-containing particles) in patients with diabetes and mixed dyslipidaemia enrolled in the BANTING (Evaluation of Evolocumab Efficacy in Diabetic Adults With Hypercholesterolemia/Mixed Dyslipidemia) and BERSON (Safety and Efficacy of Evolocumab in Combination With Statin Therapy in Adults With Diabetes and Hyperlipidemia or Mixed Dyslipidemia) studies.[265,266]

Alirocumab significantly reduced the rate of a composite of CV death, MI, stroke, or hospitalization for unstable angina in the sub-group of patients with ACS with T2DM ($n = 5444$) of the ODYSSEY OUTCOMES trial.[267] Alirocumab on top of the maximum tolerated statin dose was also more effective than ezetimibe, fenofibrate, or non-lipid-lowering therapy in reducing non-HDL-C and other atherogenic lipids in patients with diabetes enrolled in the ODYSSEY DM-DYSLIPIDEMIA (Efficacy and Safety of Alirocumab Versus Usual Care on Top of Maximally Tolerated Statin Therapy in Patients With Type 2 Diabetes and Mixed Dyslipidemia) trial.[268]

A meta-analysis by Khan *et al.* did not show a significant association between PCSK9 inhibitors and new-onset diabetes (HR 1.00; 95% CI, 0.93–1.07; $P = 0.96$; $I^2 = 0\%$), while confirming a modest risk of incident diabetes with statins only (HR 1.10; 95% CI, 1.05–1.15; $P < 0.001$; $I^2 = 0\%$).[269]

5.5.2.4. Fibrates and other TG-lowering drugs

Potential use of fibrates to reduce TG levels is quite limited, due to the risk of myopathy if given with statins and the little benefit demonstrated in RCTs, aside from sub-group analysis including subjects with very high TG levels.[200,270,271] Pemafibrate is a new selective peroxisome proliferator-activated receptor-α modulator with a superior benefit-risk balance compared with conventional fibrates.[272] A phase 3 trial determining the efficacy of pemafibrate in preventing MACE in patients with diabetes has been terminated early for futility.[273]

If TGs remain elevated even with a statin-based regimen, icosapent ethyl, a stable ester of eicosapentaenoic acid, might be preferred over other omega–3 fatty acids at the dose of 2 g twice a day (b.i.d.), due to its favourable impact on CV outcomes reported in the REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl—Intervention Trial) trial, where benefit was consistent in patients with (58%) and without diabetes ($P_{int} = 0.29$).[274] This benefit remained significant even considering a slight increase of LDL-C and high-sensitivity C-reactive protein due to the effect of mineral oil in the placebo arm.[275,276]

5.5.3. Novel cholesterol-lowering drugs

5.5.3.1. Inclisiran

Inclisiran inhibits hepatic synthesis of PCSK9 with a long-lasting effect.[277] Patients on statins with high LDL-C levels and ASCVD or at least one ASCVD risk equivalent were included in the two phase 3 trials ORION-10 and ORION-11 (Inclisiran for Participants With Atherosclerotic Cardiovascular Disease and Elevated Low-density Lipoprotein Cholesterol), and obtained a further 50% reduction of LDL-C with inclisiran.[278] This benefit was consistent in patients with diabetes in both trials, and CV outcome endpoints are currently being tested in a phase 3 trial enrolling patients with ASCVD (ORION-4 trial).[279]

5.5.3.2. Bempedoic acid

Bempedoic acid is a pro-drug that reduces cholesterol synthesis by inhibiting adenosine triphosphate (ATP) citrate lyase, with very limited musculoskeletal-related side effects.[280] In the CLEAR (Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen) Harmony trial, adding bempedoic acid to statins significantly reduced LDL-C levels (–16.5%) in patients with ASCVD or familial hypercholesterolaemia, with consistent results in the sub-group of patients with diabetes (–19.1%).[267] Bempedoic acid did not induce new-onset diabetes or worsen diabetes as shown by a subsequent meta-analysis.[281] High CV risk patients who were unable or unwilling to take statins have been included in the CLEAR Outcomes study and randomized to bempedoic acid or placebo. Among the 6992 patients assigned to the active arm of the study 45% had T2DM. Bempedoic acid was associated with a significantly lower incidence of the four-component composite primary endpoint of CV death, non-fatal MI, non-fatal stroke, or coronary revascularization and a higher incidence of some adverse events (gout and cholelithiasis) at the 40.6 month follow-up. Of note, the data were only released just before finalising these Guidelines and could thus not be included.[282]

Recommendation Table 11 — Recommendations for the management of dyslipidaemia in patients with diabetes

Recommendations	Class[a]	Level[b]
Lipid targets		
In patients with T2DM at moderate CV risk, an LDL-C target of <2.6 mmol/L (<100 mg/dL) is recommended.[248,249]	I	A
In patients with T2DM at high CV risk, an LDL-C target of <1.8 mmol/L (<70 mg/dL) and LDL-C reduction of at least 50% is recommended.[248,249]	I	A

Continued

In patients with T2DM at very high CV risk, an LDL-C target of <1.4 mmol/L (<55 mg/dL) and LDL-C reduction of at least 50% is recommended.[248,249]	I	B
In patients with T2DM, a secondary goal of a non-HDL-C target of <2.2 mmol/L (<85 mg/dL) in very high CV risk patients and <2.6 mmol/L (<100 mg/dL) in high CV risk patients is recommended.[283–285]	I	B
Lipid-lowering treatment		
Statins are recommended as the first-choice LDL-C-lowering treatment in patients with diabetes and above-target LDL-C levels. Administration of statins is defined based on the CV risk profile of the patients and the recommended LDL-C (or non-HDL-C) target levels.[247–249]	I	A
A PCSK9 inhibitor is recommended in patients at very high CV risk, with persistently high LDL-C levels above target despite treatment with a maximum tolerated statin dose, in combination with ezetimibe, or in patients with statin intolerance.[267,286]	I	A
If the target LDL-C is not reached with statins, combination therapy with ezetimibe is recommended.[259,260]	I	B
If a statin-based regimen is not tolerated at any dosage (even after re-challenge), a PCSK9 inhibitor added to ezetimibe should be considered.[287,288]	IIa	B
If a statin-based regimen is not tolerated at any dosage (even after re-challenge), ezetimibe should be considered.[259,260]	IIa	C
High-dose icosapent ethyl (2 g b.i.d.) may be considered in combination with a statin in patients with hypertriglyceridaemia[c].[274]	IIb	B

b.i.d., twice a day; CV, cardiovascular; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; T2DM, type 2 diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.
[c]Hypertriglyceridaemia: triglycerides 150–499 mg/dL, according to the inclusion of the REDUCE-IT trial.

5.6. Antithrombotic therapy and diabetes

Several mechanisms contribute to platelet activation and coagulation in diabetes (*Figure 11*). The pharmacology of different antithrombotic agents can be found in the Supplementary data online, *Section 2.7* and *Figures S1–5*.

5.6.1. Patients without a history of symptomatic atherosclerotic cardiovascular disease or revascularization

The largest meta-analysis on 95 000 individual participant data (IPD) of patients at average CV risk (0.57% MACE/year) from six RCTs, included 3818 (4%) patients with diabetes. In the whole cohort, low-dose acetylsalicylic acid (ASA) significantly reduced MACE vs. control (absolute risk reduction [ARR] 0.06%/year; $P = 0.0001$), while increasing major extracranial bleed (0.10% vs. 0.07%/year; absolute risk increase 0.03%/year; $P < 0.0001$; Supplementary data online, *Table S11*).[291] A similar proportional benefit-risk profile was also observed in the diabetes subgroup (Supplementary data online, *Table S11*).

The ASCEND (A Study of Cardiovascular Events iN Diabetes) trial was the largest, adequately powered, placebo-controlled RCT testing low-dose ASA in patients with T1DM or T2DM ($n = 15\,480$) with no evident CVD.[292] Over 7.4 years, ASA significantly reduced serious vascular events vs. placebo (8.5% vs. 9.6%, respectively; RR 0.88; 95% CI, 0.79–0.90; $P = 0.01$; number needed to treat [NNT] 91; Supplementary data online, *Table S11*), with a relative benefit similar to the previous meta-analysis.[291] Bleeding Academic Research Consortium (BARC) type 3–5 bleeding (Supplementary data online, *Figure S6*) occurred in 4.1% vs. 3.2% of patients in the ASA and placebo arms, respectively (RR 1.29; 95% CI, 1.09–1.52; $P = 0.003$; number needed to harm [NNH] 111). ASA-associated major bleeding excess was largely gastrointestinal, without differences in fatal, intracranial, and ocular bleeding. The NNT/NNH ratio was 0.8. The pre-specified sub-group analysis based on vascular risk score at baseline was consistent with the overall population (Supplementary data online, *Figure S7*).

The benefit of ASA in the ASCEND trial was observed on top of statins (75% of patients) and/or anti-hypertensive (~60% of patients) drugs.[292] Consistently, a recent IPD meta-analysis of 18 162 patients with multiple CV risk factors and no previous ASCVD (risk 1.7%/year) showed a significant benefit of low-dose ASA, incremental to lipid- and BP-lowering drugs. This was also observed in a diabetes subgroup (Supplementary data online, *Table S11*).[293]

A 9.2-year follow-up analysis of the ASCEND trial excluded harm of ASA on incident dementia, with a trend towards a reduction (HR 0.89; 95% CI, 0.75–1.06) confirmed by a meta-analysis of three large primary prevention RCTs (HR 0.92; 95% CI, 0.84–1.01; $P = 0.09$).[294]

Large, observational, prospective data suggest CAC as a non-invasive biomarker to identify asymptomatic patients at the highest risk of ASCVD or revascularization, with or without diabetes, who may largely benefit from ASA.[295] Ongoing trials are testing the relevance of CAC score and related thresholds in improving primary prevention, including in asymptomatic patients with diabetes.[296–298]

In summary, in patients with diabetes and no history of symptomatic ASCVD or revascularization, ASA (75–100 mg o.d.) may be considered to prevent the first severe vascular event. However, in patients with diabetes with asymptomatic ASCVD (including documented CAD confirmed by imaging) and a higher CV risk, the net benefit of platelet inhibition by ASA may be higher and thus, therapy needs to be individualized.

Recommendation Table 12 — Recommendations for patients with diabetes without a history of symptomatic atherosclerotic cardiovascular disease or revascularization

Recommendation	Class[a]	Level[b]
In adults with T2DM without a history of symptomatic ASCVD or revascularization, ASA (75–100 mg o.d.) may be considered to prevent the first severe vascular event, in the absence of clear contraindications.[c,292,293]	IIb	A

ASA, acetylsalicylic acid; ASCVD, atherosclerotic cardiovascular disease; o.d., once daily; T2DM, type 2 diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.
[c]High risk of bleeding due to gastrointestinal haemorrhage or peptic ulcer within the previous 6 months, active hepatic disease (such as cirrhosis, active hepatitis), or history of ASA allergy.

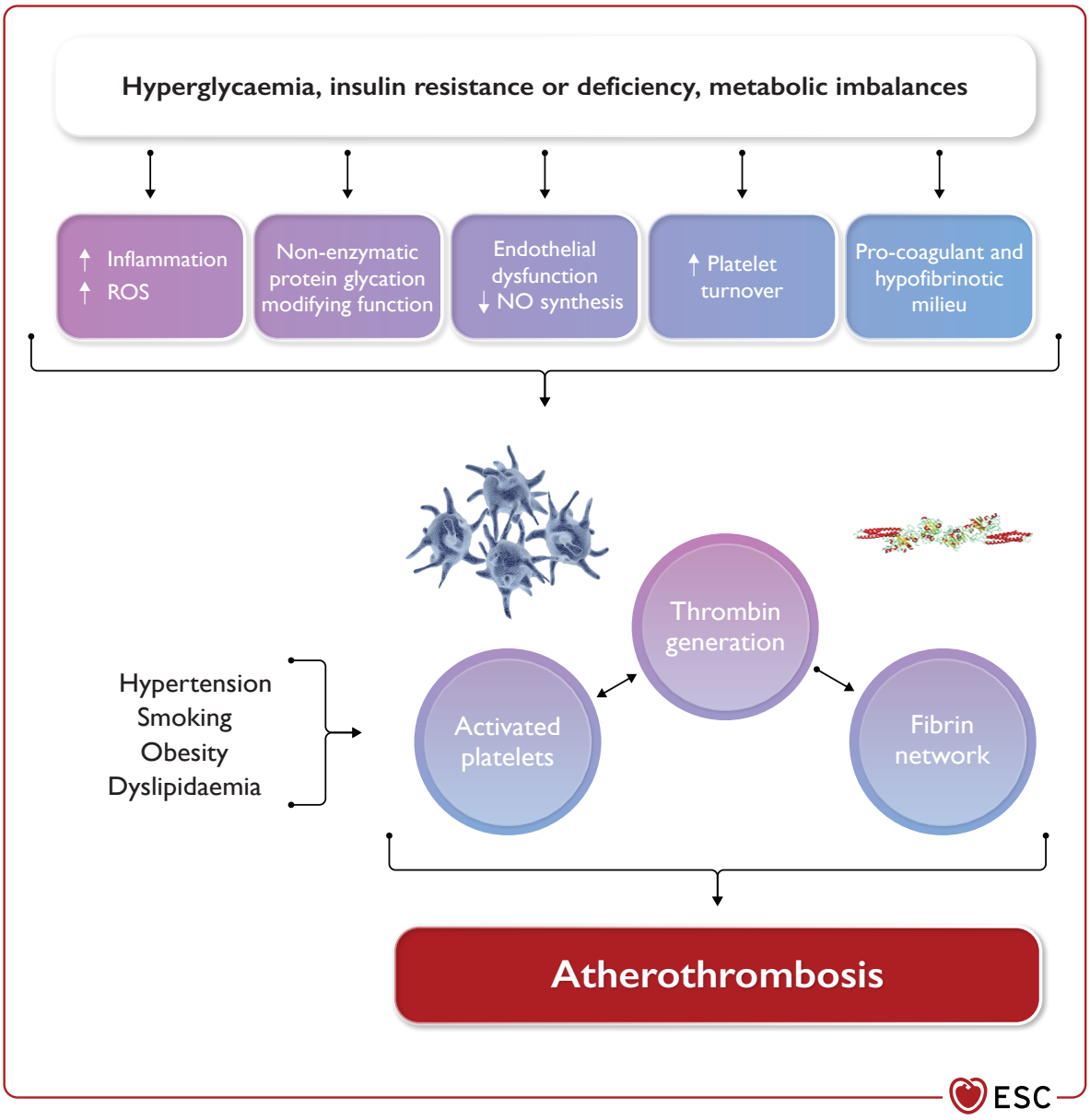

Figure 11 Mechanisms contributing to altered platelet activation and atherothrombosis in patients with diabetes. ↑, increase; ↓, decrease; NO, nitric oxide; ROS, reactive oxygen species.[289,290] The figure depicts the major determinants contributing to platelet activation leading to atherothrombosis in patients with diabetes. An inflammatory environment, metabolic changes, endothelial dysfunction and altered platelet turnover result in a platelet population characterized by enhanced activation, increased thrombin generation, and suppression of the fibrinolytic system. Thrombin release by platelets and *de novo* generation through activation of the coagulation pathway further amplify platelet activation and result in fibrin network formation, thus playing a pivotal role in the increased risk of thrombosis in individuals with diabetes.

5.6.2. Patients with atherosclerotic cardiovascular disease and/or revascularization without an indication for long-term oral anticoagulation

5.6.2.1. Chronic coronary syndromes

Patients with diabetes and documented significant CAD or with prior revascularization are at very high CV risk, and low-dose ASA (75–100 mg o.d.) is recommended, although *ad hoc* RCTs are lacking.[48,299] Both the ADAPTABLE (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term) and CURRENT-OASIS 7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent EveNTs/Optimal Antiplatelet Strategy for InterventionS) trials showed comparable efficacy of a lower dose (75–100 mg o.d.) and a three- to four-fold higher (300–325 mg o.d.) ASA dose in both chronic coronary syndrome (CCS) and ACS.[300,301]

Clopidogrel provides an alternative in ASA-intolerant patients or can be combined with low-dose ASA (clopidogrel 75 mg o.d. and ASA 75–100 mg o.d.) as dual antiplatelet therapy (DAPT) in patients with CCS undergoing percutaneous coronary intervention (PCI).

The THEMIS (Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study) trial tested the efficacy and safety of adding the $P2Y_{12}$ inhibitor ticagrelor (60 mg b.i.d.) or placebo to ASA (75–150 mg o.d.) in 19 220 patients with diabetes and a history of PCI or coronary artery bypass graft (CABG), or a documented stenosis (≥50%) in at least one coronary artery, and no previous MI or stroke

(Supplementary data online, *Table S11*).[302] Over a median 3.3 years of follow-up, the primary efficacy outcome of CV death, MI, or stroke showed a marginal 10% RR reduction by ticagrelor vs. placebo, while both Thrombolysis in Myocardial Infarction (TIMI) major and intracranial bleeding were significantly increased. The pre-specified sub-groups of CABG or previous PCI showed a benefit-risk profile consistent with the entire trial.[302,303] The NNT/NNH ratio was 1.5. Thus, an unfavourable benefit-risk profile is associated with adding ticagrelor to ASA in this setting.

The COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial enrolled 27 395 patients with stable ASCVD (previous MI, symptomatic CAD, and/or PAD). Low-dose ASA combined with very low-dose rivaroxaban (2.5 mg b.i.d.) was superior to ASA and placebo in preventing MACE (4.1% vs. 5.4%, respectively; HR 0.76; 95% CI, 0.66–0.86; $P < 0.001$; NNT 77).[304] International Society on Thrombosis and Haemostasis-defined major bleeding, but not fatal or intracranial bleeding, was increased (1.9% vs. 3.1%, respectively; HR 1.70; 95% CI, 1.40–2.05; $P < 0.001$; NNH 83), with an NNT/NNH ratio of 0.9 (Supplementary data online, *Figure S7*). The proportional benefit-risk profile of the diabetes sub-group (38% of all patients) was similar to the overall population. Based on these data, adding very low-dose rivaroxaban to low-dose ASA for long-term prevention of serious vascular events should be considered in patients with diabetes and CCS or symptomatic PAD without high bleeding risk.[304,305] Data are available up to 47 months of ASA plus very low-dose rivaroxaban exposure; beyond this time, continuation should be determined on an individual basis and with regular evaluation of thrombotic vs. bleeding risks.

5.6.2.2. Acute coronary syndrome

5.6.2.2.1. Peri-procedural management. Peri-procedural management of patients with ACS or undergoing PCI, which may include glycoprotein IIb/IIIa inhibitors, cangrelor, heparins, or bivalirudin, is detailed in the 2018 ESC/European Association for Cardio-Thoracic Surgery (EACTS) Guidelines on myocardial revascularization.[299,306–308]

5.6.2.2.2. Post-procedural management. In patients with ACS undergoing PCI, 12 months' DAPT with low-dose ASA and prasugrel or ticagrelor was superior to DAPT with clopidogrel in the diabetes sub-group of the respective RCTs, with a benefit-risk profile similar to the overall trial populations (Supplementary data online, *Tables S12–13*).[309–312] With the limitations of a subgroup analysis, patients with diabetes on DAPT with low-dose ASA and prasugrel tended to have a more favourable benefit-risk profile.[312] The open-label ISAR-REACT 5 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) trial randomized 4018 patients with ACS to prasugrel or ticagrelor added to ASA.[313] Prasugrel was superior to ticagrelor in reducing MACE without increasing major bleeding, with similar effects in the sub-group of patients with diabetes ($n = 892$; 22%; Supplementary data online, *Table S12*).[313]

Thus, DAPT, i.e. low-dose ASA with prasugrel or ticagrelor are preferred to DAPT with clopidogrel in patients with diabetes and ACS (Supplementary data online, *Table S12*),[309–312] unless the patient is deemed at very high bleeding risk. Of note, patients with T2DM have a reduced generation of the active metabolite of clopidogrel compared with patients without diabetes (Supplementary data online, *Section 2.7*).[323,324] Notably, previous intracranial bleeding contraindicates patients to both prasugrel and ticagrelor.

In patients with diabetes and ACS who do not undergo cardiac revascularization, DAPT with ASA (75–100 mg o.d.) and a $P2Y_{12}$ receptor inhibitor, preferably ticagrelor over clopidogrel, is recommended for 12 months.[314,315]

5.6.2.2.3. Prolonging DAPT post-ACS. The GLOBAL-LEADERS (A Clinical Study Comparing Two Forms of Antiplatelet Therapy After Stent Implantation) trial failed to show superior efficacy or safety of 24 months of ticagrelor monotherapy post-ACS vs. the standard 12-month DAPT followed by 12-month low-dose ASA monotherapy in the overall and diabetes (25% of all patients) cohorts.[316]

The PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin) trial compared prolonged ticagrelor therapy (60 or 90 mg b.i.d.) with placebo added to low-dose ASA in patients with an MI 1–3 years before study entry and additional CV risk factors.[317] Reduced-dose ticagrelor (60 mg) decreased MACE compared with placebo (7.77% vs. 9.04%, respectively; HR 0.84; 95% CI, 0.74–0.95; $P = 0.004$; NNT 79), with no heterogeneity with respect to the diabetes sub-group, whereas it significantly increased TIMI major bleeding (2.3% vs. 1.06%, respectively; HR 2.32; 95% CI, 1.68–3.21; NNH 81), dyspnoea, serious adverse events, and drug discontinuation rates.[317] Based on these data, DAPT prolonged beyond 12 months should be considered up to 3 years in patients with diabetes who have tolerated DAPT without major bleeding.[63,317,318] The median follow-up across all trials on prolonging full-dose DAPT was 18 months (interquartile range 12–24 months), with a maximum DAPT exposure no longer than 36 months.[318] No sufficient safety and efficacy data are available for DAPT with reduced-dose ticagrelor beyond 3 years, especially considering the significant TIMI major bleeding increase of the association (Supplementary data online, *Figure S6*).[317,319]

5.6.2.2.4. Shortening or de-escalating DAPT post-ACS in diabetes. No evidence supports shortening or de-escalating DAPT post-ACS specifically in patients with diabetes, since RCTs on shorter DAPT duration followed by ASA or a $P2Y_{12}$ inhibitor monotherapy are relatively small, often with non-inferiority design for efficacy, relatively low power, and wide non-inferiority margins. In addition, these RCTs had primary endpoints combining minor bleeding with traditional efficacy outcomes, efficacy outcomes including not only MACE, and diabetes sub-groups that contain few patients and events, especially on the major hard endpoints (Supplementary data online, *Table S13*).[320,321] Moreover, large, superiority RCTs have failed to show a higher efficacy of routine platelet-function testing in guiding antiplatelet therapy post-PCI.[322,322a] Of note, the TROPICAL-ACS (Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment For Acute Coronary Syndromes) trial 'de-escalating' $P2Y_{12}$ inhibition from prasugrel to clopidogrel after 2 weeks of DAPT based on platelet function testing showed an upper HR limit for MACE of 1.93 in the diabetes sub-group (HR 1.17; 95% CI, 0.71–1.93). Moreover, CV death was significantly increased in sub-groups with diabetes vs. without diabetes in the 'de-escalating' arm (HR 2.42; 95% CI, 0.61–9.67; $P_{int} = 0.04$), thus suggesting harm from de-escalation compared with standard recommended DAPT.[321] In addition, patients with diabetes form less of the clopidogrel active metabolite resulting in less platelet inhibition (Supplementary data online, *Section 2.7*).[323,324]

Thus, shortening or de-escalating DAPT below 12 months is not recommended in patients with diabetes in the 12 months post-ACS. Current evidence does not support platelet function testing to adjust DAPT.

Figure 12 summarizes recommendations in patients with diabetes and ACS or CCS undergoing PCI or CABG.

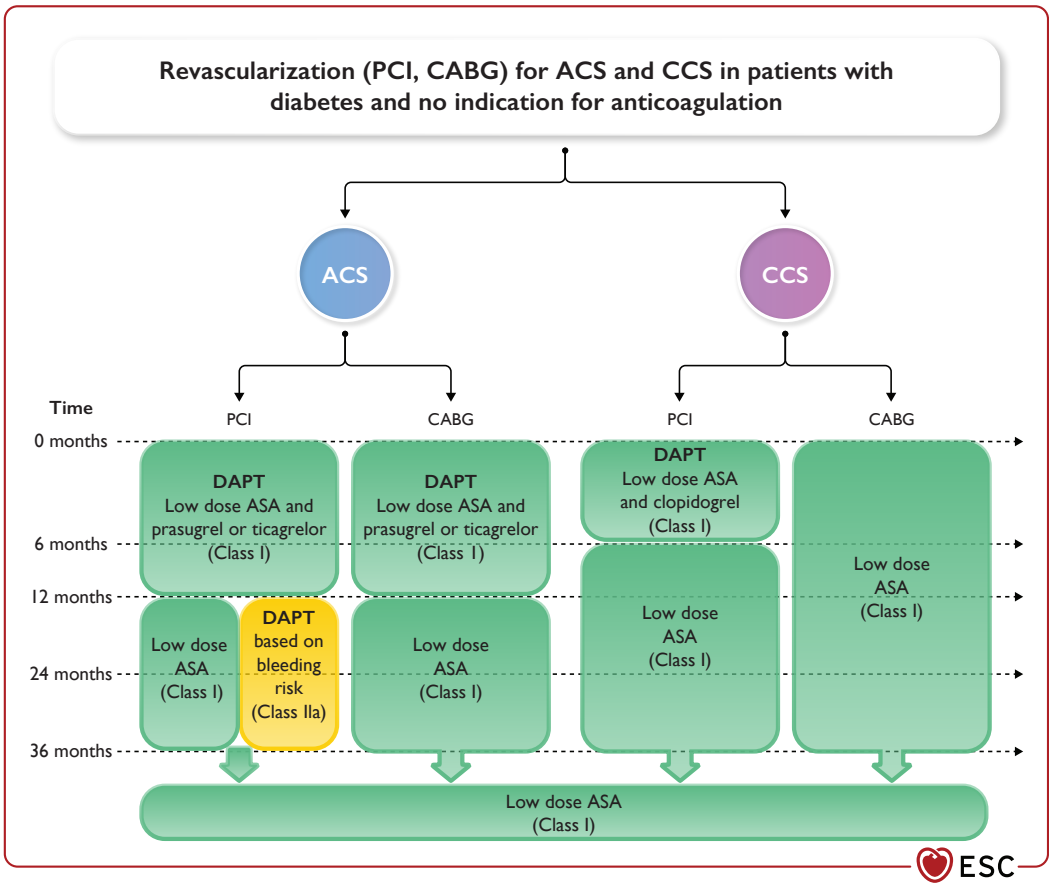

Figure 12 Recommendations for antiplatelet therapy in patients with diabetes with acute or chronic coronary syndrome undergoing percutaneous coronary intervention or coronary artery bypass grafting without indications for long-term oral anticoagulation. ACS, acute coronary syndrome; ASA, acetylsalicylic acid; CABG, coronary artery bypass graft; CCS, chronic coronary syndrome; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention.

Recommendation Table 13 — Recommendations for antithrombotic therapy in patients with diabetes and acute or chronic coronary syndrome without indications for long-term oral anticoagulation

Recommendations	Class[a]	Level[b]
ASA at a dose of 75–100 mg o.d. is recommended in patients with diabetes and previous MI or revascularization (CABG or stenting).[291,325,326]	I	A
In patients with ACS and diabetes who undergo PCI, a $P2Y_{12}$ receptor inhibitor (ticagrelor or prasugrel) is recommended in addition to ASA (75–100 mg o.d.), maintained over 12 months.[310–312,314]	I	A
Clopidogrel 75 mg o.d. following appropriate loading (e.g. 600 mg or at least 5 days already on maintenance therapy) is recommended in addition to ASA for 6 months following coronary stenting in patients with CCS, irrespective of stent type, unless a shorter duration is indicated due to the risk or occurrence of life-threatening bleeding.[327–332]	I	A
Clopidogrel is recommended as an alternative in case of ASA intolerance.[333]	I	B
In patients with diabetes and ACS treated with DAPT who are undergoing CABG and do not require long-term OAC therapy, resuming a $P2Y_{12}$ receptor inhibitor as soon as deemed safe after surgery and continuing it up to 12 months is recommended.[315,334,335]	I	C
Prolonging DAPT beyond 12 months after ACS should be considered for up to 3 years in patients with diabetes who have tolerated DAPT without major bleeding complications.[c,317,318,336]	IIa	A
Adding very low-dose rivaroxaban[d] to low-dose ASA for long-term prevention of serious vascular events should be considered in patients with diabetes and CCS or symptomatic PAD without high bleeding risk.[304,305]	IIa	B

ACS, acute coronary syndrome; ASA, acetylsalicylic acid; b.i.d., twice a day; CABG, coronary artery bypass graft; CCS, chronic coronary syndrome; DAPT, dual antiplatelet therapy; MI, myocardial infarction; OAC, oral anticoagulant; o.d., once daily; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention.
[a]Class of recommendation.
[b]Level of evidence.
[c]In case of ticagrelor, a reduced dose (60 mg b.i.d.) should be used.[317]
[d]Rivaroxaban 2.5 mg b.i.d.

Continued

5.6.3. Patients with atherosclerotic cardiovascular disease and/or revascularization requiring long-term oral anticoagulation

In patients requiring long-term oral anticoagulants (OACs; e.g. those with AF) undergoing PCI for ACS or CCS, DAPT with clopidogrel is combined with full-dose OACs (triple antithrombotic therapy [TAT]). Combined antithrombotic drugs, while effective, increase major bleeding risk.[337,338] RCTs have compared TAT with dual antithrombotic therapy (DAT) combining an OAC mostly with clopidogrel, in patients with AF and ACS or post-PCI (Supplementary data online, *Table S14*). These RCTs have some common features: a primary outcome of safety comprising moderate-to-major, often BARC-defined, bleeding (Supplementary data online, *Figure S7*); efficacy (including CV death, MI, stroke, as well as revascularization, and/or stent thrombosis) as a secondary endpoint, often with a non-inferiority comparison; relatively short follow-up (6–14 months); and limited sample size with few patients with diabetes (28–37% across RCTs; Supplementary data online, *Table S14*).[339–342] Thus, these RCTs are underpowered to assess both the efficacy of DAT and the safety of major bleeding of TAT in patients with diabetes. Moreover, two meta-analyses suggest significantly higher MI and stent thrombosis rates with DAT vs. TAT (Supplementary data online, *Table S14*).[343,344] The lack of high-quality evidence on efficacy, meta-analyses suggesting some harm, and the underlying high CV and stent thrombosis risk in patients with diabetes, indicate that TAT duration should be cautiously and systematically evaluated for both thrombotic and bleeding risks in the individual patient with diabetes.

Recommendation Table 14 — Recommendations for antithrombotic therapy in patients with diabetes and acute or chronic coronary syndrome and/or post-percutaneous coronary intervention requiring long-term oral anticoagulation

Recommendations	Class[a]	Level[b]
In patients with AF and receiving antiplatelet therapy, eligible for anticoagulation, and without a contraindication,[c] NOACs are recommended in preference to a VKA.[339,340,343]	I	A
In patients with ACS or CCS and diabetes undergoing coronary stent implantation and having an indication for anticoagulation, triple therapy with low-dose ASA, clopidogrel, and an OAC is recommended for at least 1 week, followed by dual therapy with an OAC and a single, oral, antiplatelet agent.[339–342,344,345]	I	A
In patients with ACS or CCS and diabetes undergoing coronary stent implantation and having an indication for anticoagulation, prolonging triple therapy with low-dose ASA, clopidogrel, and an OAC should be considered up to 1 month if the thrombotic risk outweighs the bleeding risk in the individual patient.[341–344]	IIa	C
In patients with ACS or CCS and diabetes undergoing coronary stent implantation and having an indication for anticoagulation, prolonging triple therapy with low-dose ASA, clopidogrel, and an OAC up to 3 months may be considered if the thrombotic risk outweighs the bleeding risk in the individual patient.[341–344]	IIb	C

ACS, acute coronary syndrome; AF, atrial fibrillation; CCS, chronic coronary syndrome; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; VKA, vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.
[c]Contraindications to NOACs are prosthetic mechanical heart valve, mitral stenosis, and creatinine clearance below the approved threshold for the specific NOAC.

5.6.4. Preventing gastrointestinal bleeding

Large observational studies or head-to-head RCTs show similar rates of gastrointestinal and non-gastrointestinal major bleeding for single antiplatelet therapy (SAPT) with low-dose ASA or a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor).[337,338,346–350] Thus, gastrointestinal mucosal bleeding appears to be due to pre-existing mucosal lesions associated with defective primary haemostasis secondary to platelet inhibition, rather than with a specific antiplatelet drug. A meta-analysis showed that gastroprotectant drugs significantly reduce the risk of gastrointestinal bleeding in patients on single or combined antithrombotic drugs.[351] This benefit was also observed in the pre-specified subgroup of 6732 patients with diabetes in the COMPASS trial, consistent with large population studies on proton pump inhibitors and OACs (either vitamin K antagonist [VKA] or non-vitamin K antagonist oral anticoagulant [NOACs]).[352] Regarding CV safety, the composite of MI, stroke, CV death, CHD, and acute limb ischaemia was similar between pantoprazole and placebo, as was the rate of new-onset diabetes.[337,351–355]

Recommendation Table 15 — Recommendations for gastric protection in patients with diabetes taking antithrombotic drugs

Recommendations	Class[a]	Level[b]
When antithrombotic drugs are used in combination, proton pump inhibitors are recommended to prevent gastrointestinal bleeding.[337,347,348,351–353,355]	I	A
When a single antiplatelet or anticoagulant drug is used, proton pump inhibitors should be considered to prevent gastrointestinal bleeding, considering the bleeding risk of the individual patient.[338,347,348,351,352]	IIa	A
When clopidogrel is used, omeprazole and esomeprazole are not recommended for gastric protection.[356]	III	B

[a]Class of recommendation.
[b]Level of evidence.

5.7. Multifactorial approach to risk-factor management in diabetes

Optimal risk factor and lifestyle management, as well as early identification and treatment of comorbidities, is a cornerstone of treatment for T2DM.[357–359] The Swedish National Diabetes Registry revealed a clear improvement of clinical outcomes by each risk factor within the target range (HbA1c, LDL-C, albuminuria, smoking, and SBP).[360] In patients with advanced disease, e.g. T2DM and established microalbuminuria, an intensive, target-driven, multifactorial therapy (Steno-2 study; targets: HbA1c <6.5%, total cholesterol <4.5 mmol/L [175 mg/dL], and BP <130/80 mmHg) resulted in 50% fewer microvascular and macrovascular events after 7.8 years of follow-up.[361] Long-term follow-up (21 years from baseline) showed significantly reduced end-stage renal disease combined with death (HR 0.53; 95% CI, 0.35–0.80), and risk of HF hospitalization reduced by 70%.[362] Overall, this resulted in a 7.9 year gain of life expectancy.[363]

These positive effects were not observed in the clinical intervention trials of intensified, multifactorial treatment for T2DM in primary care and early in the disease trajectory. The ADDITION (Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care) trial showed that microvascular or macrovascular events were not significantly reduced after 5 or 10 years (17% and 13% reduction, respectively), while intervention only slightly improved HbA1c.[364,365] In accordance, the J-DOIT3 (Japan Diabetes Optimal Integrated Treatment Study for 3 Major Risk Factors of Cardiovascular Diseases) trial in patients with T2DM aged 45–69 years revealed a non-significant trend towards a reduced primary composite outcome (non-fatal MI, stroke, revascularization, or all-cause death; HR 0.81; 95% CI, 0.63–1.04; $P = 0.094$) with intensive vs. conventional therapy.[366] *Post-hoc* analyses showed that only cerebrovascular events were reduced (HR 0.42; 95% CI, 0.24–0.74; $P = 0.002$), while no differences were seen for all-cause death and coronary events. In addition, the Look AHEAD trial, introducing lifestyle intervention in patients with obesity and T2DM with 10 years' follow-up, did not demonstrate a reduction in the composite CV outcome.[56]

Key problems in optimally treating patients with T2DM and CVD are the low rate of detection of T2DM in patients with CVD, the low referral rate to diabetes specialists, and the difficulty of prolonged adherence to medication or lifestyle interventions in this patient group. The EUROASPIRE V survey reported that many patients with CVD (29.7%) had known diabetes, while 41.1% of those with unknown T2DM were dysglycaemic.[367] Of patients with known diabetes, 31% had been advised to attend a diabetes clinic, though only 24% attended. Only 58% of dysglycaemic patients were prescribed all cardio-protective drugs, and use of SGLT2 inhibitors or GLP-1 RAs was limited (3% and 1%, respectively).[367] A BP target <140/90 mmHg was achieved in only 61% of patients with newly detected T2DM, and in 54% of patients with previously known T2DM.[34] An LDL-C target <1.8 mmol/L was only achieved in 18% and 28% of patients, respectively. This was explained by low prescription rates of the combination of all cardio-protective drugs (antiplatelet therapy, beta-blockers, RAS inhibitors, and statins) in only 55% of patients with newly detected T2DM, and in 60% of patients with previously known T2DM.[34] The concept of a polypill, e.g. containing aspirin, ramipril, and atorvastatin, may even improve clinical events in secondary cardiovascular prevention.[368]

Furthermore, adherence to lifestyle intervention fades over time, with continuously increasing body weight after 1 year.[56] To overcome adherence failures, the 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice outlines a stepwise approach to treating risk factors and intensifying treatment to help physicians and patients pursue risk-factor targets, taking into account patient profiles and preferences, ensuring targets are a part of a shared decision-making process involving healthcare professionals and patients.[48] This stepwise approach starts with assessing CVD risk in all patients with diabetes, including glycaemic state and lifestyle risk-factor profile (*Figure 13*). CVD risk stratification should be individually adapted according to comorbidities, e.g. CAD, HF, AF, or PAD, as well as age, frailty, and sex. This includes discussing individual preferences with the patient, particularly regarding lifestyle strategies and potential treatment benefits. Particularly in the field of T2DM, studies have shown benefits of a stepwise approach to intensify treatment, and it appears that attaining treatment goals is similar, side effects are fewer, and patient satisfaction is significantly higher with such an approach.[369,370] Supporting evidence comes from the Italian Diabetes and Exercise Study 2, which showed that a behavioural intervention strategy compared with standard care resulted in a sustained increase in physical activity and decrease in sedentary time among patients with T2DM.[371]

To achieve a high adherence and optimization of target goals, clinician–patient communication is crucial and should include a personalized approach explaining background and targets to improve understanding and encourage lifestyle changes and drug-therapy adherence. Aside from the disease entity, including symptoms, the patient's ability to adopt a healthy lifestyle depends on individual cognitive and emotional factors, educational level, socioeconomic factors, and mental health. Perceived susceptibility to illness and the anticipated severity of the consequences are also prominent components of patients' motivation.[372] Patients can be motivated by motivational interviewing including the Open-ended questions, Affirmation, Reflective listening, and Summarizing (OARS) and Specific, Measurable, Achievable, Realistic, Timely (SMART) principles.[372–374] Multidisciplinary behavioural approaches that combine the knowledge and skills of different caregivers are recommended.[104] Adding exercise intervention combined with psychological support to diet recommendations is more effective than diet education alone.[375] Assessing depression and depressive symptoms is important in patients with CVD and T2DM, as adequate treatment improves adherence.[376,377]

Mobile phone applications may improve adherence to both medication and behavioural changes, but more evidence, particularly in patients with CVD and T2DM, is needed.[378] Regarding the education method, individual education is more effective than face-to-face or web and mobile phone education.[375] Whether a tailored and automated text message (SMS) support programme may improve glycaemic control in adults with poorly controlled diabetes is equivocal.[379]

Recommendation Table 16 — Recommendations for a multifactorial approach in patients with type 2 diabetes with and without cardiovascular disease

Recommendations	Class[a]	Level[b]
Identifying and treating risk factors and comorbidities early is recommended.[357,358]	I	A
A multifactorial approach to managing T2DM with treatment targets is recommended.[361]	I	B
Multidisciplinary behavioural approaches that combine the knowledge and skills of different caregivers are recommended.[104,380]	I	C
Principles of motivational interviewing should be considered to induce behavioural changes.[372–374]	IIa	C
Telehealth may be considered to improve risk profile.[378,379]	IIb	B

T2DM, type 2 diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.

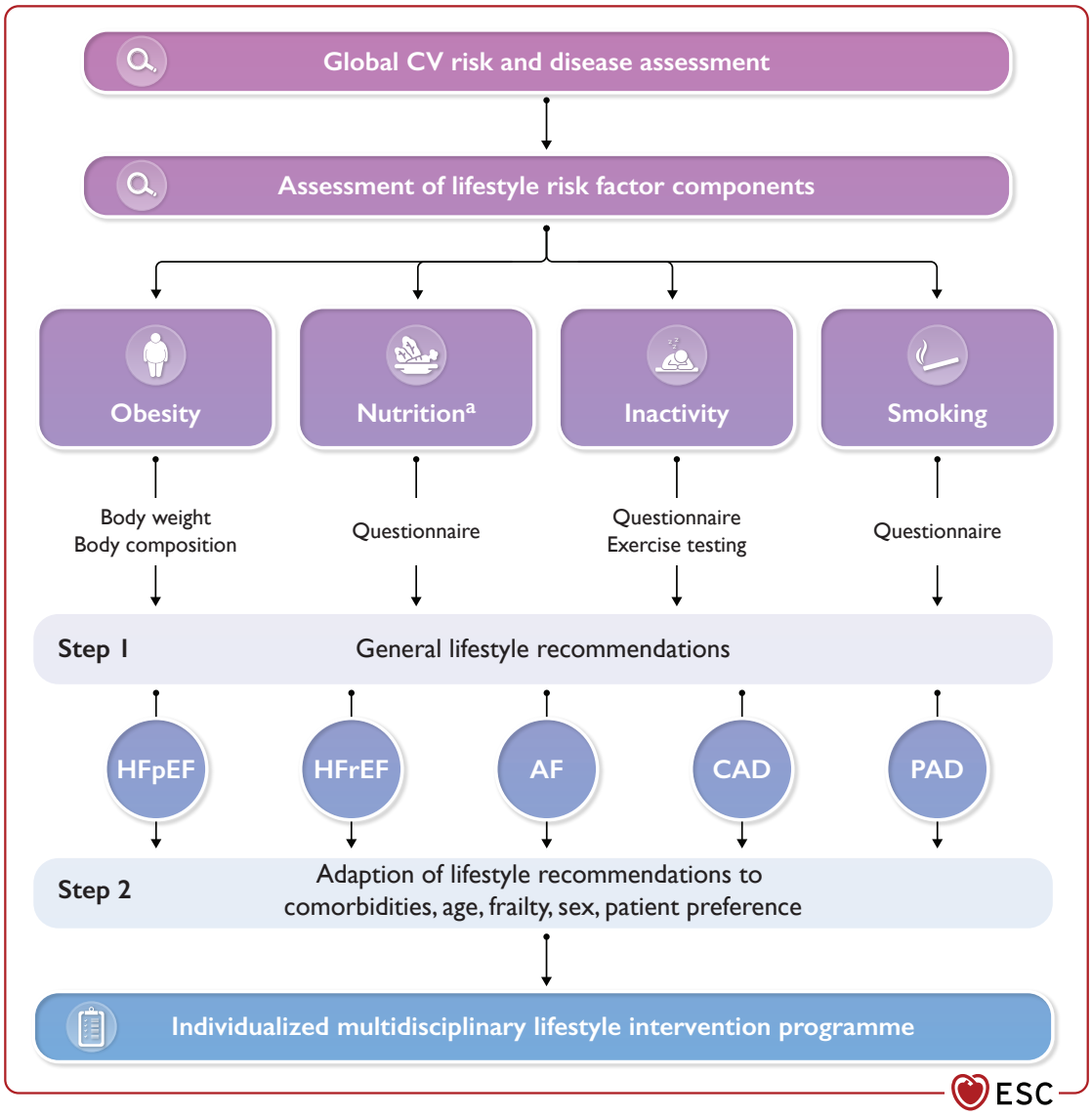

Figure 13 Assessment of lifestyle risk-factor components and stepwise lifestyle recommendations in patients with diabetes. AF, atrial fibrillation; CAD, coronary artery disease; CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; PAD, peripheral arterial diseases. [a]Nutrition includes components on quality and quantity of nutritional components, as well as alcohol consumption.

6. Management of coronary artery disease and diabetes

6.1. Chronic coronary syndromes and diabetes

6.1.1. Clinical presentation

Diabetes is a well-established risk factor for ischaemic heart disease (IHD), and CAD accounts for 40–80% of deaths in patients with T2DM.[148,359,381] In patients with CCS, T2DM is also associated with an increased risk of the combined outcome (CV death, MI, or stroke) with an adjusted HR of 1.28.[39] Studies show that clinical symptoms of CAD in patients with diabetes are often less severe and atypical in presentation. In the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial in patients with angiographically confirmed CAD and a mean diabetes duration of 10.4 years, typical angina, anginal equivalent, or a combination of both were observed in 19%, 21%, and 42% of patients, respectively, whereas 18% remained asymptomatic.[382,383] In 510 asymptomatic patients with diabetes without prior CVD, computed tomography (CT) revealed calcifications indicating the presence of coronary atherosclerosis in 46% of patients.[384] An even higher prevalence of CAD was found in an autopsy study of asymptomatic decedents with diabetes.[385]

6.1.2. Screening and diagnosis

For details about sensitivity, specificity, and pre-test probability of each procedure in the assessment of CHD, we refer to the 2019 ESC Guideline on chronic coronary syndromes.[299]

Screening for asymptomatic CAD in diabetes remains controversial. Various RCTs evaluating the impact of routine screening for CAD in asymptomatic patients with diabetes and no history of CAD showed

no differences in CV outcomes at follow-up in those who underwent routine screening compared with standard recommendations.[386–388] Data from a meta-analysis of five RCTs with 3299 asymptomatic patients with diabetes showed non-invasive CAD screening significantly reduced the rate of any cardiac event by 27% (RR 0.73; 95% CI, 0.55–0.97; $P = 0.028$), driven by a non-significant reduction in non-fatal MI (RR 0.65; $P = 0.062$) and hospitalization for HF (RR 0.61; $P = 0.1$). Still, given the limitations of this analysis (e.g. different screening modalities, heterogenous patient populations), non-invasive, routine screening for CAD in asymptomatic patients is not recommended.[389] Moreover, in a recently published RCT involving men aged 65–74 years, routine CVD screening did not significantly reduce the incidence of death from any cause after a median follow-up of 5.6 years, also in a pre-specified diabetes sub-group.[296]

6.1.3. Management

The comprehensive management of patients with diabetes and established CAD should start with a healthy lifestyle and reducing or eliminating modifiable risk factors such as obesity, hypertension, or dyslipidaemia. The goal of pharmacotherapy should be to substantially reduce serious CV events. Targets and pharmacotherapy for glycaemia, BP, and LDL-C levels are addressed in the respective sections (*Section 5.2, 5.4, and 5.5*).

6.1.3.1. Pharmacotherapy

6.1.3.1.1. Glucose-lowering medication. Based on the results of various CVOTs, SGLT2 inhibitors and/or GLP-1 RAs are recommended in patients with T2DM and CAD to reduce CV events (*Section 5.3*).

6.1.3.1.2. Other medications. Due to the diffuse nature of CAD, some patients with diabetes are not amenable to revascularization. Symptom relief might then be achieved by increasing myocardial oxygen supply with long-acting nitrates or CCBs, or by decreasing oxygen demand with the help of beta-blockers, non-dihydropyridine CCBs, ranolazine, or ivabradine. Note that none of these medications improves mortality or the rate of ischaemic events. Beta-blockers with a simultaneous vasodilatory effect (e.g. carvedilol, nebivolol, labetalol) may be preferred due to their neutral or positive metabolic impact.[390–392] Ranolazine, a drug that reduces myocardial ischaemia at the cellular level, also has the unique effect of reducing HbA1c, especially in patients with poor metabolic control.[393,394] In normotensive patients with diabetes and CAD, ACE-Is or ARBs are also recommended to reduce the risk of CV events, especially in patients with HF or CKD.[395–397]

6.1.3.2. Revascularization

In patients with diabetes, the indications for myocardial revascularization are the same as those in patients without diabetes, the essential aspects of which are reported in the 2018 ESC/EACTS Guidelines on myocardial revascularization and 2019 ESC Guideline on chronic coronary syndromes.[299,308] A detailed description of the evidence from outcome trials on revascularization in patients with diabetes can be found in Supplementary data online, *Section 3.1.1*. In brief, given the current knowledge, in patients with diabetes and multivessel disease, CABG with arterial grafts is preferred over complex PCI, providing that patient characteristics (e.g. frailty, cerebrovascular disease) are considered.[398] PCI with newer-generation drug-eluting stents (DES), whenever possible, is acceptable for patients with less-extensive disease (i.e. single-vessel disease or two-vessel disease not involving the left anterior descending, and those with SYNTAX Score ≤22). Thus, the extent of CAD, lesion complexity, and the risk of major surgery are key points in the decision-making process. Because most of the trials on revascularization contained patients with T2DM, current Guidelines cannot easily be applied to patients with T1DM. It has now been demonstrated that CABG is also superior to PCI in patients with T1DM and multivessel CAD.[399]

Recommendation Table 17 — Recommendations for revascularization in patients with diabetes

Recommendations	Class[a]	Level[b]
It is recommended that similar revascularization techniques are implemented (e.g. the use of DES and the radial approach for PCI, and the use of the left internal mammary artery as the graft for CABG) in patients with and without diabetes.[400]	I	A
Myocardial revascularization in CCS is recommended when angina persists despite treatment with anti-anginal drugs or in patients with a documented large area of ischaemia (>10% LV).[382,401,402,402a]	I	A
Complete revascularization is recommended in patients with STEMI without cardiogenic shock and with multivessel CAD.[403–405]	I	A
Complete revascularization should be considered in patients with NSTE-ACS without cardiogenic shock and with multivessel CAD.[406,407]	IIa	C
Routine immediate revascularization of non-culprit lesions in patients with MI and multivessel disease presenting with cardiogenic shock is not recommended.[408]	III	B

CABG, coronary artery bypass graft; CAD, coronary artery disease; CCS, chronic coronary syndrome; DES, drug-eluting stents; LV, left ventricle; MI, myocardial infarction; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.

For recommendations for revascularization according to the extent of CAD, see the 2018 ESC/EACTS Guidelines on myocardial revascularization and the 2019 ESC Guideline on chronic coronary syndromes.[299,308]

6.2. Acute coronary syndromes and diabetes

6.2.1. Clinical presentation and diagnosis

Diabetes is a frequent comorbidity in patients hospitalized for ACS, with an increasing prevalence over the last decade and a high mortality rate.[409] Among patients presenting with ST-elevation myocardial infarction (STEMI), ~25% have a history of diabetes and more than 40% show a previously undiagnosed T2DM or pre-diabetes.[410] Patients with diabetes more often present with non-typical symptoms compared with those without diabetes, and this impacts prompt diagnosis and treatment.[411] Moreover, patients with diabetes frequently have multivessel disease and multiple coronary lesions, with a higher percentage of highly vulnerable atherosclerotic plaques associated with impaired microvasculature vasodilation.[412,413]

6.2.2. Management

6.2.2.1. Pharmacotherapy

Patients with diabetes and ACS, despite the poor prognosis and high prevalence of comorbidities, are less likely to receive appropriate treatment such as revascularization, reperfusion, or adequate DAPT.[414,415] One of the reasons may be the lack of typical symptoms.[416] While few studies have focused exclusively on patients with diabetes, analyses of studies indicate that guideline-directed pharmacotherapy provides patients with diabetes similar or improved absolute benefits compared with patients without diabetes, yet the incidence of events remains constantly higher in those with vs. without diabetes.[309,312,417]

6.2.2.2. Glucose control in patients with acute coronary syndrome

Patients with ACS and hyperglycaemia on admission to hospital have a higher risk of death than patients with ACS without hyperglycaemia, irrespective of diabetes status.[418] Mortality correlates more strongly to the blood glucose level than to the presence of diabetes.[419,420] Thus, early assessment of blood glucose level is strongly recommended in all subjects, although there is insufficient evidence that intensive glycaemic control improves prognosis. The DIGAMI 1 trial showed that early, tight glycaemic control with intravenous (i.v.) insulin–glucose infusion followed by subcutaneous injections significantly reduced 1-year mortality compared with conventional glucose-lowering treatment.[421] Conversely, the DIGAMI 2 study, and later pooled analyses of studies on insulin–glucose infusions did not confirm this observation.[146,422] Other studies have shown that adequate glycaemic control improves the prognosis of patients with ACS, while also demonstrating the importance of avoiding hypoglycaemia, which is strongly associated with worse outcomes.[423,424] A criticism of previous studies is the inadequate characterization of glycaemia, with most studies analysing HbA1c as the glycaemic marker, when both hypoglycaemia and glycaemic variability potentially have a role in CV pathology.

Considering all evidence, it is best to attempt moderately tight glycaemic control while avoiding hypoglycaemia in the early hours of ACS. Continuous insulin infusion should be limited to cases where the optimal glycaemic control cannot be achieved otherwise; blood glucose level should be maintained <11.1 mmol/L (<200 mg/dL) or <10.0 mmol/L (<180 mg/dL) according to some recommendations.[425–427] Frequent blood glucose testing, preferably hourly during the acute ACS phase, will help to avoid hypoglycaemia. CGM provides comprehensive glucose data while being more convenient than blood glucose testing, and the LIBERATES (Improving Glucose Control in Patients with Diabetes Following Myocardial Infarction: The Role of a Novel Glycaemia Monitoring Strategy) RCT in 141 insulin- or sulphonylurea-treated patients with T2DM and ACS showed that CGM over 3 months significantly reduced hypoglycaemic exposure compared with traditional capillary glucose testing, while being equally effective at reducing HbA1c.[428] In the EMMY (Impact of EMpagliflozin on cardiac function and biomarkers of heart failure in patients with acute MYocardial infarction) trial, 467 patients were randomized to empagliflozin 10 mg or placebo within 72 h of PCI for acute MI.[429] The study drug was associated with a significantly greater N-terminal pro-B-type natriuretic peptide (NT-proBNP) reduction over 26 weeks (primary outcome) and a significant improvement in echocardiographic LV parameters, without demonstrating any difference in adverse events of special interest including metabolic acidosis and diabetic ketoacidosis.[429]

It should be noted that hyperglycaemia in the acute phase of ACS might reflect stress hyperglycaemia and is not enough to diagnose diabetes. These patients should be further evaluated after discharge (*Section 3*).

Recommendation Table 18 — Recommendations for glycaemic control in patients with diabetes and acute coronary syndrome

Recommendations	Class[a]	Level[b]
It is recommended to assess glycaemic status at initial evaluation in all patients with ACS.[141,367,430]	I	B
It is recommended to frequently monitor blood glucose levels in patients with known diabetes or hyperglycaemia (defined as glucose levels ≥11.1 mmol/L or ≥200 mg/dL).	I	C
Glucose-lowering therapy should be considered in patients with ACS with persistent hyperglycaemia, while episodes of hypoglycaemia should be avoided.[423,424]	IIa	C

ACS, acute coronary syndrome.
[a]Class of recommendation.
[b]Level of evidence.

Antithrombotic medication in patients with ACS is further described in *Section 5.6*.

6.2.2.3. Reperfusion strategies in ST-elevation myocardial infarction

The therapeutic strategy in patients with diabetes presenting with STEMI should not differ from that for patients without diabetes. As for the general population, prognosis is determined by early and effective reperfusion. Since patients with diabetes are more likely to present with atypical symptoms, reperfusion is often undertaken late.[431] Although, patients with diabetes and STEMI, compared with those without diabetes, are older, more often have multivessel disease and concomitant conditions, and are less likely to receive reperfusion therapy. Diabetes is regarded as an independent risk factor of early and late mortality.[432–436] Primary angioplasty, performed in a timely fashion, also provides the best clinical outcomes in patients with diabetes.[437] Several recent studies indicate the clinical benefit of early, single-stage, complete revascularization in patients with non-ST-elevation ACS (NSTE-ACS) and early complete revascularization in those with STEMI and multivessel disease.[403–407,432–435] The exception is patients in cardiogenic shock, where it is recommended to limit the procedure to the infarct-related artery.[408] Adding proton pump inhibitors, limiting use of glycoprotein IIb/IIIa inhibitors, and avoiding heparin in patients on OACs if the international normalized ratio (INR) >2.5 are recommended.[308]

6.2.2.4. Optimal timing of invasive strategy in non-ST-elevation acute coronary syndrome

In patients with diabetes and NSTE-ACS, the indications and timing of revascularization should not differ from those for patients without diabetes.[438] Multiple studies have indicated that an early invasive strategy is beneficial in high-risk sub-groups.[439–442] Since diabetes is one of the risk factors of poor prognosis, patients with diabetes may benefit significantly more from the early invasive approach than those without diabetes.[417,443] In a meta-analysis of eight RCTs in patients with NSTE-ACS, which compared an early vs. a delayed invasive strategy, diabetes, elevated troponin, and a Global Registry of Acute Coronary Events (GRACE) risk score >140 predicted lower mortality in the early invasive arm.[444]

According to current guidelines, an immediate invasive strategy (within 2 h from admission) should be applied to very high-risk patients, mostly with electrical or haemodynamic instability.[426] These patients were excluded from all major randomized ACS trials. In addition, patients with severe symptoms, refractory to medical therapy, or those with electrocardiogram (ECG) signs suggesting the left main stem as a culprit vessel should be promptly referred for coronary angiography. An early invasive strategy (within 24 h) should be applied to high-risk patients, especially those with markedly elevated troponins, dynamic ST/T-segment changes, transient ST-segment elevation, or a GRACE risk score >140.

6.3. Ischaemia with no obstructive coronary artery disease in diabetes

Details on the role of ischaemia with no obstructive CAD are outlined in the Supplementary data online, *Section 3.2*.

7. Heart failure and diabetes

7.1. Definition and pathophysiology

Heart failure is not a single pathological disease but a clinical syndrome with current or prior symptoms and/or signs caused by a structural and/or functional cardiac abnormality. It is corroborated by elevated natriuretic peptides and/or objective evidence of cardiogenic pulmonary or systemic congestion from diagnostic modalities, such as imaging or invasive haemodynamic measurements.[445]

Heart failure is one of the most common initial manifestations of CVD in patients with T2DM, and may present as HFpEF, heart failure with mildly reduced ejection fraction (HFmrEF), or HFrEF (*Table 9*).[446]

Major causes of HF in diabetes are IHD (*Section 6*), hypertension (*Section 5.3*), direct or indirect effects of hyperglycaemia, and obesity and related factors on the myocardium.[447,448] IHD is often accelerated, severe, diffuse, and silent, and increases the risk of MI and ischaemic myocardial dysfunction.[449–452] Observational data have also identified that lower-extremity artery disease (LEAD), longer diabetes duration, ageing, increased BMI, and CKD (*Section 9*) are associated with HF in patients with diabetes (*Table 10*).[449–452] Complex pathophysiological mechanisms may be responsible for the development of myocardial dysfunction, even in the absence of IHD or hypertension.[453] For decades, the concept of diabetic cardiomyopathy has been discussed, with mostly experimental and smaller observational studies suggesting its presence; however, its existence has so far not been confirmed.[447,454–458]

Table 9 Heart failure phenotypes according to ejection fraction distribution[445]

HF phenotype	HFpEF	HFmrEF	HFrEF
Criterion 1	Symptoms and/or signs[a]	Symptoms and/or signs[a]	Symptoms and/or signs[a]
Criterion 2	LVEF ≥50%	LVEF 41–49%	LVEF ≤40%
Criterion 3	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction or raised filling pressures, including raised natriuretic peptides	None	None

HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction.
[a]Symptoms include, for example, breathlessness, ankle swelling, and fatigue. Signs may not be present at an early stage or in patients receiving diuretics.

Table 10 Risk factors for developing heart failure in patients with diabetes

Cardiac risk factors	Ischaemic heart disease Myocardial infarction Hypertension Valvular heart disease Arrhythmias
Non-cardiac risk factors	Age Chronic kidney disease Increased body mass index Longer duration of diabetes Smoking Alcohol excess

7.2. Epidemiology and prognosis

Diabetes is an important risk factor for HF.[459] Observational studies have consistently demonstrated a two- to four-fold increased risk of HF in individuals with diabetes compared with those without diabetes.[460–463] The prevalence of chronic HF increases steadily with age for patients with and without diabetes. Patients with T2DM develop chronic HF more often and earlier in life than those without T2DM, with an incremental risk inversely associated with age; for example, in one study, the incident rate ratio was 11.0 (95% CI, 5.6–21.8) for those <45 years, declining to 1.8 (95% CI, 1.6–2.2) for those aged 75–84 years, reflecting the higher absolute HF risk in elderly patients without diabetes.[463] Unrecognized HF is frequent in T2DM: a cross-sectional study in patients aged ≥60 years with T2DM without known HF using a standardized diagnostic work-up, including medical history, physical examination, ECG, and echocardiography, indicated that HF was present in 28% of patients (~25% HFrEF and ~75% HFpEF).[460–464]

Vice versa, HF is associated with a diabetes incidence of 20–30 per 1000 person-years in the first 5 years following HF hospitalization, which is substantially higher than for adults in the general population (10.1 per 1000 person-years).[465,466] A large, pan-European registry found that ~36% of all outpatients with stable HF had diabetes, while in patients hospitalized for acute HF for whom i.v. therapy (inotropes, vasodilators, or diuretics) was needed, diabetes was present in up to 50%.[467,468] In addition, available data from observational studies demonstrate that diabetes prevalence in patients with HF is similar, irrespective of LVEF category.[469,470]

A significant association exists between diabetes and a higher risk of adverse outcomes in patients with HF, with the greatest incremental risk associated with diabetes observed in patients with HFrEF.[467,471–475] However, CV mortality, including death caused by worsening HF, is also 50–90% higher in patients with HF and diabetes compared

with HF patients without diabetes, regardless of HF phenotype.[471,475–477] In patients with acute HF, for whom i.v. therapy (inotropes, vasodilators, or diuretics) was needed, diabetes was associated with higher risk of in-hospital death, 1 year all-cause death, and 1 year HF re-hospitalization.[468,478]

7.3. Screening and diagnosis

Patients with diabetes are at risk of HF but not all patients with diabetes will develop HF.[479] Given that the prognosis of patients with both co-morbidities is worse, it is of utmost importance to screen all patients with diabetes for HF to allow early implementation of life-saving therapies. To predict the HF risk among outpatients with T2DM, the WATCH-DM (Weight [BMI], Age, Hypertension, Creatinine, HDL-C, Diabetes control [fasting plasma glucose], QRS duration, MI, and CABG) risk score has been developed.[480] Each increment of 1 unit in the risk score is associated with a 24% higher HF risk within 5 years. In addition, a biomarker-based risk score including high-sensitivity cardiac troponin T ≥6 ng/L, NT-proBNP ≥125 pg/mL, high-sensitivity C-reactive protein ≥3 mg/L, and LV hypertrophy by ECG (with one point for each abnormal parameter) demonstrated good discrimination and calibration for predicting 5- and 10-year HF risk among patients with diabetes. The highest 5-year risk of HF was noted among those with scores ≥3.[481] The Heart Failure Association of the ESC reviewed the clinical evidence and value of further biomarker testing and currently recommends no further testing.[482]

To detect transition from being at risk of HF to developing HF, the following regular evaluation is recommended in patients with diabetes (*Figure 14*):

- Regularly, a systematic survey for HF symptoms (breathlessness, dyspnoea on exertion, orthopnoea, paroxysmal nocturnal dyspnoea, nocturia, fatigue, tiredness, increased time to recover following exercise) or signs (weight gain, peripheral oedema, elevated jugular venous pulse, rales, hepatojugular reflux, third heart sound, or laterally

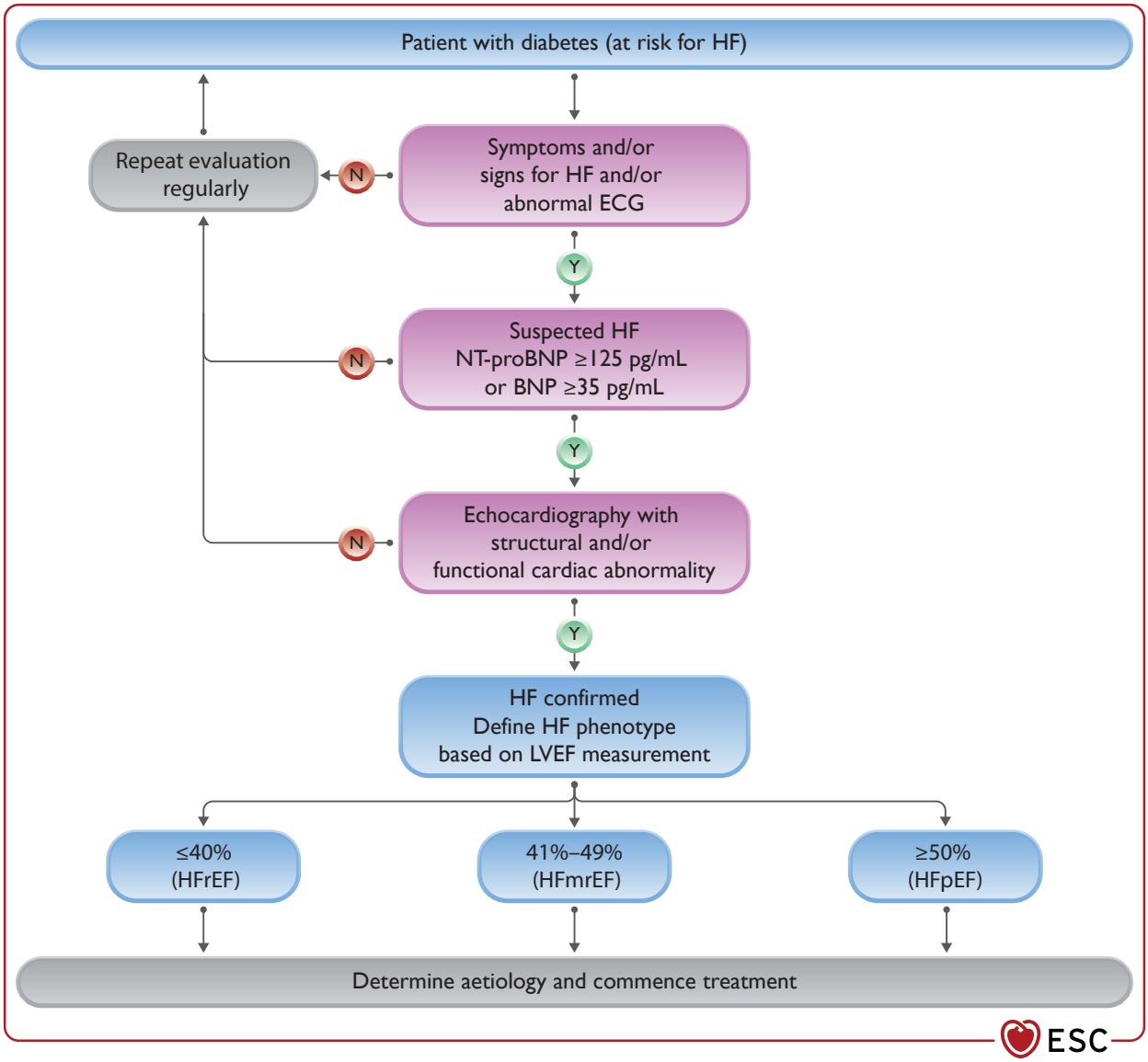

Figure 14 Diagnostic algorithm for heart failure in patients with diabetes. BNP, B-type natriuretic peptide; ECG, electrocardiogram; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

displaced apical impulse) is recommended. For more details, see the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure.[445]

If one or more of the symptoms or signs above is present, HF can be suspected, and the following diagnostic tests are recommended:

- Measurement of natriuretic peptides is recommended, if available. Values below the following cut-offs make the diagnosis of HF unlikely and other diagnoses should be considered:[483–485]
  - B-type natriuretic peptide (BNP) <35 pg/mL (threshold in AF: <105 pg/mL).
  - NT-proBNP <125 pg/mL (threshold in AF: <365 pg/mL).

However, natriuretic peptide concentrations may be disproportionately low in patients with obesity or in women, and disproportionately high in patients with advanced CKD, advanced age, or AF.[486,487] Still, elevated concentrations support the diagnosis of HF and may guide further cardiac investigation.[488]

- ECG is recommended to detect abnormalities such as AF, signs of LV hypertrophy, Q waves, or widened QRS, each of which may be a sign of HF.[489]
- Echocardiography is recommended to assess cardiac function including LV function, chamber size, LV hypertrophy, regional wall motion abnormalities (that may suggest CAD), right ventricular function, estimated pulmonary pressure, valvular function, and markers of diastolic dysfunction. Transthoracic echocardiography may be considered to detect HF in patients with diabetes if other risk factors arise.
- Chest X-ray is recommended to investigate other causes of dyspnoea (e.g. pulmonary disease). It may provide supportive evidence of HF (e.g. cardiomegaly, pulmonary congestion, pleural effusion).
- Routine blood tests (including full blood count, urea, creatinine, and electrolytes, thyroid and liver function, lipids, and iron status (ferritin and transferrin saturation) are recommended to differentiate HF from other conditions, to obtain prognostic information, and to guide potential therapy. Additional diagnostic tests should be considered if other specific diagnoses are suspected (e.g. amyloidosis).
- If HF is confirmed, additional diagnostic tests are recommended as summarized in the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure.[445]

Recommendation Table 19 — Recommendations for heart failure screening and diagnosis in patients with diabetes

Recommendations	Class[a]	Level[b]
Evaluating for heart failure		
If HF is suspected, it is recommended to measure BNP/NT-proBNP.[485]	I	B
Systematic survey for HF symptoms and/or signs of HF is recommended at each clinical encounter in all patients with diabetes.	I	C
Diagnostic tests in all patients with suspected heart failure		
12-lead ECG is recommended.	I	C
Transthoracic echocardiography is recommended.	I	C
Chest radiography (X-ray) is recommended.	I	C
Routine blood tests for comorbidities are recommended, including full blood count, urea, creatinine and electrolytes, thyroid function, lipids, and iron status (ferritin and TSAT).	I	C

ECG, electrocardiogram; HF, heart failure; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TSAT, transferrin saturation.
[a]Class of recommendation.
[b]Level of evidence.

7.4. Treatment of heart failure in patients with diabetes

7.4.1. Treatment of heart failure with reduced ejection fraction

Treatment of HFrEF encompasses therapeutic lifestyle modifications, as well as pharmacological and device therapies with benefits confirmed in RCTs, in which 30–40% of patients had diabetes. Treatment effects of medications and devices for HFrEF have been consistently demonstrated to not differ in patients with vs. without diabetes. Importantly, while the RR reductions are consistently similar for those with and without diabetes, given the higher absolute HFrEF clinical risk associated with diabetes, the ARR in patients with diabetes is typically higher, yielding a lower NNT for benefit among patients with diabetes.

The cornerstone of treatment for HFrEF is pharmacotherapy alongside lifestyle interventions, which should be implemented before considering device therapy. The recent 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure recommend starting quadruple therapy (angiotensin receptor–neprilysin inhibitor [ARNI]/ACE-I, MRA, beta-blocker, SGLT2 inhibitor).[445] These four foundational treatments should be initiated early, as much of the benefits are seen within 30 days of starting treatment, and adding new drugs yields greater benefits than up-titrating existing drug classes. In the STRONG-HF (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP testinG, of Heart Failure Therapies) trial, 1078 patients with acute HF, 29% of whom had diabetes at baseline, were assigned to either high-intensity care with up-titration of treatments to 100% of recommended doses within 2 weeks of discharge or to usual care.[490] Safety and tolerability were assessed at weeks 1, 2, 3, and 6 by full physical examination and laboratory assessments of NT-proBNP, sodium, potassium, glucose, kidney function, and haemoglobin measures. The study was stopped early due to a greater than expected between-group difference. The primary endpoint, consisting of 180-day re-admission to hospital due to HF or all-cause death, was significantly reduced in the high-intensity group, with a RR reduction of 34% (HR 0.66; 95% CI, 0.50–0.86) with similar incidences of serious adverse events. Of note, no sub-group analysis exists on patients with diabetes. Based on these data, an intensive strategy of early initiation of evidence-based treatment (SGLT2 inhibitors, ARNI/ACE-Is, beta-blockers, and MRAs), with rapid up-titration to trial-defined target doses and frequent follow-up visits in the first 6 weeks following discharge from a HF hospitalization is recommended to reduce re-admissions or mortality. The sequence of therapy initiation should be based on the individual patient phenotype taking into account BP, heart rhythm, and heart rate, as well as kidney function and risk of hyperkalaemia. While the start dose of SGLT2 inhibitors is the same as the target dose, ARNI/ACE-Is, beta-blockers, and MRAs should be started at low dose and up-titrated to the maximum tolerated dose. For more details on HFrEF therapy, please refer to the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure.[445] The

specific characteristics for patients with diabetes are presented in the following sections.

7.4.1.1. Sodium–glucose co-transporter-2 inhibitors

Two randomized placebo-controlled trials have investigated the effect of an SGLT2 inhibitor compared with placebo added to optimal medical therapy (OMT) in patients with HFrEF with and without diabetes. The DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial included patients if they were in New York Heart Association (NYHA) class II–IV, had an LVEF ≤40% despite OMT, and had elevated NT-proBNP (in sinus rhythm ≥600 pg/mL, in AF ≥900 mg/mL, or ≥400 pg/mL if they had been hospitalized for HF within the previous 12 months). Patients with T1DM or an eGFR <30 mL/min/1.73 m^2 were excluded. Therapy with dapagliflozin 10 mg o.d. vs. placebo reduced the risk of the primary outcome, a composite of worsening HF (hospitalization or an urgent visit resulting in i.v. therapy for HF) or CV death, by 26% (HR 0.74; 95% CI, 0.65–0.85). In addition, dapagliflozin reduced all-cause mortality (HR 0.83; 95% CI, 0.71–0.97) and improved symptoms, physical function, and quality of life in patients with HFrEF.[491,492] All of the clinical benefits observed were independent of baseline diabetes status and background glucose-lowering therapy, and consistent across the spectrum of HbA1c.[491,493] The EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction) trial evaluated empagliflozin vs. placebo and included patients with HFrEF with and without diabetes, with NYHA class II–IV, and LVEF ≤40% despite OMT, an eGFR ≥20 mL/min/1.73 m^2, and an elevated NT-proBNP (EF ≤30% or EF ≤40% and HF hospitalization within 12 months: NT-proBNP ≥600 pg/mL; EF 31–35%: NT-proBNP ≥1000 pg/mL; EF 36–40%: NT-proBNP ≥2500 pg/mL). Empagliflozin 10 mg o.d. reduced the risk of the primary outcome, a composite of CV death or HF hospitalization, by 25% vs. placebo (HR 0.75; 95% CI, 0.65–0.86).[494] This effect was consistent across patients with and without diabetes at baseline.[495] Treatment with empagliflozin improved quality of life.[496] A meta-analysis of the DAPA-HF and EMPEROR-Reduced trials showed a consistent reduction in HF hospitalization or CV death, CV death, and all-cause mortality by SGLT2-inhibitor treatment without significant heterogeneity between trials.[497]

The combined SGLT1 and -2 inhibitor sotagliflozin was investigated in patients with T2DM who were recently hospitalized for worsening HF, irrespective of their LVEF (SOLOIST-WHF [Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure] trial). Patients with an eGFR <30 mL/min/1.73 m^2 were excluded. Sotagliflozin significantly reduced the RR of the composite primary outcome (CV death, HF hospitalization, or urgent visit for HF) by 33% compared with placebo (HR 0.67; 95% CI, 0.52–0.85). The treatment effect was consistent across the spectrum of LVEF.[189]

Thus, the SGLT inhibitors dapagliflozin, empagliflozin, and sotagliflozin are recommended, in addition to OMT (with an ARNI/ACE-I, beta-blocker, and MRA), in patients with HFrEF and diabetes to reduce CV death and HF hospitalization.

Three studies have investigated whether SGLT2 inhibitors can be safely started in patients hospitalized for acute HF. The EMPA-RESPONSE-AHF (Effects of Empagliflozin on Clinical Outcomes in Patients With Acute Decompensated Heart Failure) trial randomized 80 patients with acute HF with (approximately one-third) and without diabetes to either empagliflozin or placebo for 30 days.[498] Treatment with empagliflozin did not affect visual analogue scale dyspnoea, diuretic response, NT-proBNP levels, or duration of hospital stay, but was safe, increased urinary output, and reduced a combined endpoint of worsening HF, re-hospitalization for HF, or death at 60 days compared with placebo. In the SOLOIST-WHF trial mentioned above, 1222 patients with T2DM received sotagliflozin or placebo, with a median follow-up of 9 months (trial stopped prematurely).[189] Sotagliflozin therapy, initiated before or shortly after discharge, resulted in significantly fewer deaths from CV causes and hospitalizations and urgent visits for HF than placebo, with no increase in acute kidney injury. The EMPULSE (A Study to Test the Effect of Empagliflozin in Patients Who Are in Hospital for Acute Heart Failure) trial randomized 530 hospitalized patients with and without diabetes with a primary diagnosis of acute *de novo* or decompensated HF, regardless of LVEF when clinically stable, to receive either empagliflozin or placebo. More patients treated with empagliflozin had clinical benefit (win ratio 1.36; 95% CI, 1.09–1.68) compared with placebo. This effect was consistent for acute *de novo* and decompensated chronic HF and was observed regardless of LVEF or the presence of diabetes.[499] In these trials, very few cases of euglycaemic diabetic ketoacidosis were reported; still, physicians treating patients with diabetes with SGLT2 inhibitors in this setting should be aware of this rare but potentially serious complication. Of note, misinterpreting eGFR changes can lead to inappropriate discontinuation of disease-modifying agents and should be avoided.

7.4.1.2. Angiotensin receptor–neprilysin inhibitor and angiotensin-converting enzyme inhibitors

The ARNI sacubitril/valsartan has shown superior efficacy to enalapril in reducing CV death and HF hospitalization in patients with HFrEF, with or without diabetes.[471] Patients were up-titrated to 200 mg b.i.d. sacubitril/valsartan within 2–4 weeks.[471] The beneficial effect of sacubitril/valsartan over enalapril was consistent for patients with and without diabetes and across the spectrum of baseline HbA1c.

ACE-Is were the first class of drugs shown to reduce mortality and morbidity and improve symptoms in patients with HFrEF.[500] There is no difference in efficacy in patients with and without diabetes.[501–503] As RAS inhibitors increase the risk of hyperkalaemia and may acutely compromise kidney function, routine surveillance of serum creatinine and potassium levels is advised.[504,505] However, misinterpreting eGFR changes often leads to inappropriate discontinuation of disease-modifying agents and should be avoided.[504–506]

7.4.1.3. Mineralocorticoid receptor antagonists

The steroidal MRAs spironolactone or eplerenone reduce death and HF hospitalization in patients with HFrEF, with consistent results in patients with or without diabetes.[507,508] Eplerenone is more specific for blocking aldosterone and, therefore, causes less gynaecomastia. Caution should be exercised when using MRAs in patients with impaired renal function and in those with serum potassium concentration >5.0 mmol/L. The non-steroidal MRA finerenone has not been investigated in patients with HFrEF (*Section 9*).

7.4.1.4. Beta-blockers

Beta-blockers are effective at reducing all-cause death and hospitalization for HF in patients with HFrEF, with or without diabetes.[509–512] Treatment benefits strongly support using beta-blockers in patients with HFrEF and diabetes.

7.4.1.5. Angiotensin-II receptor blockers

The place of ARBs in managing HFrEF has changed over the last few years. They are now recommended for patients who cannot tolerate ARNI or ACE-Is because of serious side effects. ARBs have similar treatment effects in patients with HFrEF with or without diabetes.[513–515]

7.4.1.6. Ivabradine

Ivabradine slows heart rate by inhibiting the I_f channel in the sinus node and is therefore only effective in patients in sinus rhythm. Ivabradine reduced the combined endpoint of CV death or HF hospitalization irrespective of diabetes status.[516]

7.4.1.7. Hydralazine and isosorbide dinitrate

There is no evidence to support the use of this fixed-dose combination therapy in all patients with HFrEF, but rather limited to self-identified Black patients as per product labelling. An RCT in self-identified Black patients with HFrEF showed that adding the combination of hydralazine and isosorbide dinitrate to conventional therapy (ACE-I, beta-blocker, MRA) reduced mortality and HF hospitalization in patients in NYHA class III–IV.[517] The beneficial effects were consistent in patients with or without diabetes.[518]

7.4.1.8. Digoxin

Digoxin may reduce the risk of HF hospitalization in patients with HFrEF treated with ACE-Is, irrespective of diabetes status.[519]

7.4.1.9. Diuretics

Despite a lack of evidence for the efficacy of either thiazide or loop diuretics in reducing CV outcomes in patients with HF, diuretics prevent and treat symptoms and signs of fluid congestion in patients with HF.[520] Importantly, a judicious use of diuretic therapy including alternating dosing over time is warranted.[521]

7.4.1.10. Device therapy and surgery

Device therapies (implantable cardioverter defibrillator [ICD], cardiac resynchronization therapy [CRT], and CRT with an implantable defibrillator [CRT-D]) have similar efficacies and risks in patients with HFrEF with or without diabetes.[522–525] These therapies should be considered according to treatment guidelines in the HFrEF population. Heart transplantation could be considered in end-stage HF, but a large, prospective study of transplanted patients indicated a decreased likelihood of 10-year survival in those with diabetes.[526]

Recommendation Table 20 — Recommendations for heart failure treatments in patients with heart failure with reduced ejection fraction and diabetes

Recommendations	Class[a]	Level[b]
Recommendations for the pharmacological treatment indicated in patients with HFrEF (NYHA class II–IV) and diabetes		
SGLT2 inhibitors (dapagliflozin, empagliflozin, or sotagliflozin[c]) are recommended in all patients with HFrEF and T2DM to reduce the risk of HF hospitalization and CV death.[189,491,494,497]	I	A
Sacubitril/valsartan or an ACE-I is recommended in all patients with HFrEF and diabetes to reduce the risk of HF hospitalization and death.[471,501,502,527]	I	A
Beta-blockers[d] are recommended in patients with HFrEF and diabetes to reduce the risk of HF hospitalization and death.[509–512,528]	I	A
MRAs[e] are recommended in patients with HFrEF and diabetes to reduce the risk of HF hospitalization and death.[507,529]	I	A
An intensive strategy of early initiation of evidence-based treatment (SGLT2 inhibitors, ARNI/ACE-Is, beta-blockers, and MRAs), with rapid up-titration to trial-defined target doses starting before discharge and with frequent follow-up visits in the first 6 weeks following a HF hospitalization is recommended to reduce re-admissions or mortality.[490]	I	B
Recommendations for other treatments indicated in selected patients with HFrEF (NYHA class II–IV) and diabetes		
Device therapy with an ICD, CRT-P, or CRT-D is recommended in patients with diabetes, as in the general population with HFrEF.[522–525]	I	A
ARBs are recommended in symptomatic patients with HFrEF and diabetes who do not tolerate sacubitril/valsartan or ACE-Is, to reduce the risk of HF hospitalization and CV death.[513–515]	I	A
Diuretics are recommended in patients with HFrEF and diabetes with signs and/or symptoms of fluid congestion to improve symptoms, exercise capacity, and HF hospitalization.[520]	I	C
Ivabradine should be considered to reduce the risk of HF hospitalization and CV death in patients with HFrEF and diabetes in sinus rhythm, with a resting heart rate ≥70 b.p.m., who remain symptomatic despite treatment with beta-blockers (maximum tolerated dose), ACE-Is/ARBs, and MRAs.[516]	IIa	B
Hydralazine and isosorbide dinitrate should be considered in self-identified Black patients with diabetes and LVEF ≤ 35% or with LVEF <45% combined with a dilated left ventricle in NYHA class III–IV despite treatment with an ACE-I (or ARNI), a beta-blocker, and an MRA, to reduce the risk of HF hospitalization and death.[517,518]	IIa	B
Digoxin may be considered in patients with symptomatic HFrEF in sinus rhythm despite treatment with sacubitril/valsartan or an ACE-I, a beta-blocker, and an MRA, to reduce the risk of hospitalization.[519]	IIb	B

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; CV, cardiovascular; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SGLT2, sodium–glucose co-transporter-2; T2DM, type 2 diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.
[c]Sotagliflozin is a dual SGLT1/2 inhibitor.
[d]Sustained-released metoprolol succinate, carvedilol, bisoprolol, and nebivolol.
[e]Spironolactone or eplerenone.

7.4.2. Treatment of heart failure with mildly reduced ejection fraction

As in other forms of HF, diuretics should be used to control congestion.[520] Results from retrospective analyses of RCTs in patients with

HFrEF or HFpEF indicate that patients with a LVEF between 40–50% benefitted from similar therapies to those with LVEF ≤40%.[445] However, to date, no definitive RCT has evaluated therapies exclusively in patients with HFmrEF. The best evidence so far derives from SGLT2-inhibitor studies. The EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure With Preserved Ejection Fraction) trial included patients with NYHA class II–IV, an LVEF >40%, and an elevated NT-proBNP (>300 pg/mL in sinus rhythm; >900 pg/mL in AF).[530] Patients with an eGFR <20 mL/min/1.73 m^2 were excluded. Compared with placebo, empagliflozin reduced the risk of the primary outcome, a composite of CV death or hospitalization for HF, by 21%, which was mainly related to a 29% lower risk of hospitalization for HF.[530] This effect was independent of diabetes status, and baseline HbA1c did not modify the effects on the primary outcome.[531] The DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure) trial included 6263 patients with NYHA class II–IV, an LVEF >40%, an elevated NT-proBNP (>300 pg/mL in sinus rhythm; >600 pg/mL in AF), and an eGFR ≥25 mL/min/1.73 m^2. Compared with placebo, dapagliflozin reduced the primary outcome, a composite of worsening HF or CV death, by 18%, which was mainly driven by a reduction in hospitalization for HF. This effect was independent of diabetes status.[532] A meta-analysis including 12 251 participants from DELIVER and EMPEROR-Preserved showed that SGLT2 inhibitors, compared with placebo, reduced a composite of CV death and first hospitalization for HF (HR 0.80; 95% CI, 0.73–0.87), with consistent reductions in both components: CV death (HR 0.88; 95% CI, 0.77–1.00) and first hospitalization for HF (HR 0.74; 95% CI, 0.67–0.83).[533]

There is no specific trial evaluating ARNI in patients with HFmrEF. The PARAGON-HF trial, which included patients with EF ≥45%, although missing its primary endpoint overall, showed significant EF-by-treatment interaction. Sacubitril/valsartan, compared with valsartan, reduced the likelihood of the primary composite outcome of CV death and total HF hospitalization by 22% in those with an LVEF below or equal to the median of 57%.[534]

7.4.3. Treatment of heart failure with preserved ejection fraction

Over the past decade, several large RCTs failed to achieve statistical significance with regard to effects on the primary outcomes in patients with HFpEF including: PEP-CHF (perindopril), CHARM-Preserved (candesartan), I-PRESERVE (irbesartan), TOPCAT (spironolactone), DIG Ancillary Trial (digoxin), and PARAGON-HF (sacubitril/valsartan).[477,534–538] As presented above in section 7.4.2, the SGLT2 inhibitors empagliflozin and dapagliflozin both reduced the RR of the primary composite outcome, CV death or hospitalization for HF, by 21% and 18%, respectively.[530,532] The treatment effect on the incidence of the primary outcome did not differ between LVEF sub-groups nor between patients with and without diabetes.[531–533] The combined SGLT1 and -2 inhibitor sotagliflozin was investigated in patients with T2DM who were recently hospitalized for worsening HF, irrespective of their LVEF (SOLOIST-WHF trial); 20.9% of the patients had an LVEF ≥50%. Sotagliflozin reduced the risk of the primary composite outcome of CV death, HF hospitalization, and urgent visit for HF by 33%, with a consistent effect across the spectrum of baseline LVEF. However, the number of events in the HFpEF group was too small to draw any firm conclusion.[189]

Diuretic therapy should be used to reduce symptoms of congestion.[520] Loop diuretics are preferred, but low-dose thiazide diuretics might be useful for managing hypertension. For treating comorbidities alongside HFpEF, refer to the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure.[445]

Recommendation Table 21 — Recommendations for heart failure treatments in patients with diabetes and left ventricular ejection fraction over 40%

Recommendations	Class[a]	Level[b]
Empagliflozin or dapagliflozin are recommended in patients with T2DM and LVEF >40% (HFmrEF and HFpEF) to reduce the risk of HF hospitalization or CV death.[530–533]	I	A
Diuretics are recommended in patients with HFpEF or HFmrEF and diabetes with signs and/or symptoms of fluid congestion to improve symptoms, exercise capacity, and HF hospitalization.[520]	I	C

CV, cardiovascular disease; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; T2DM, type 2 diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.

7.5. Safety profile of glucose-lowering agents in patients with heart failure and diabetes

For glycaemic targets in patients with diabetes, please refer to *Section 5.2*.

7.5.1. Sodium–glucose co-transporter-2 inhibitors

Sodium–glucose co-transporter-2 inhibitors (see also *Section 7.4.1.1*) have been investigated in different populations with diabetes, ranging from patients with ASCVD or multiple ASCVD risk factors to patients recently hospitalized for worsening HF, with increasing ARR for HF-related outcomes according to higher patient risk (*Figure 15*; Supplementary data online, *Table S15*).

As outlined above, in dedicated HF trials, dapagliflozin and empagliflozin reduced CV death and HF hospitalization in patients with HFrEF with or without diabetes, and sotagliflozin reduced CV death and HF hospitalization in patients with T2DM and recent hospitalization for HF of any aetiology.[189,491,494] Moreover, empagliflozin and dapagliflozin reduced the risk of CV death or HF hospitalization in patients with HFmrEF or HFpEF.[530,532]

While the EMPA-REG OUTCOME (empagliflozin) and VERTIS CV (ertugliflozin) trials investigated patients with T2DM and established ASCVD risk, the CANVAS Programme (canagliflozin) and DECLARE-TIMI 58 trial (dapagliflozin) included patients with established ASCVD or multiple ASCVD risk factors. In all of these placebo-controlled CVOTs of SGLT2 inhibitors, only a small proportion of patients had a baseline history of HF. Empagliflozin reduced the risk of HF hospitalization by 35% in patients with and without previous HF.[71] Canagliflozin also significantly reduced the risk of HF hospitalization by 33%.[151] Dapagliflozin significantly reduced the combined endpoint of CV death or HF hospitalization, a result driven mainly by lower rates of HF hospitalization.[152] This effect was independent of pre-existing HF.[540] Ertugliflozin did not reduce the combined endpoint of CV death or HF hospitalization, although there was a significant reduction in HF hospitalization and repeated hospitalizations.[154,541]

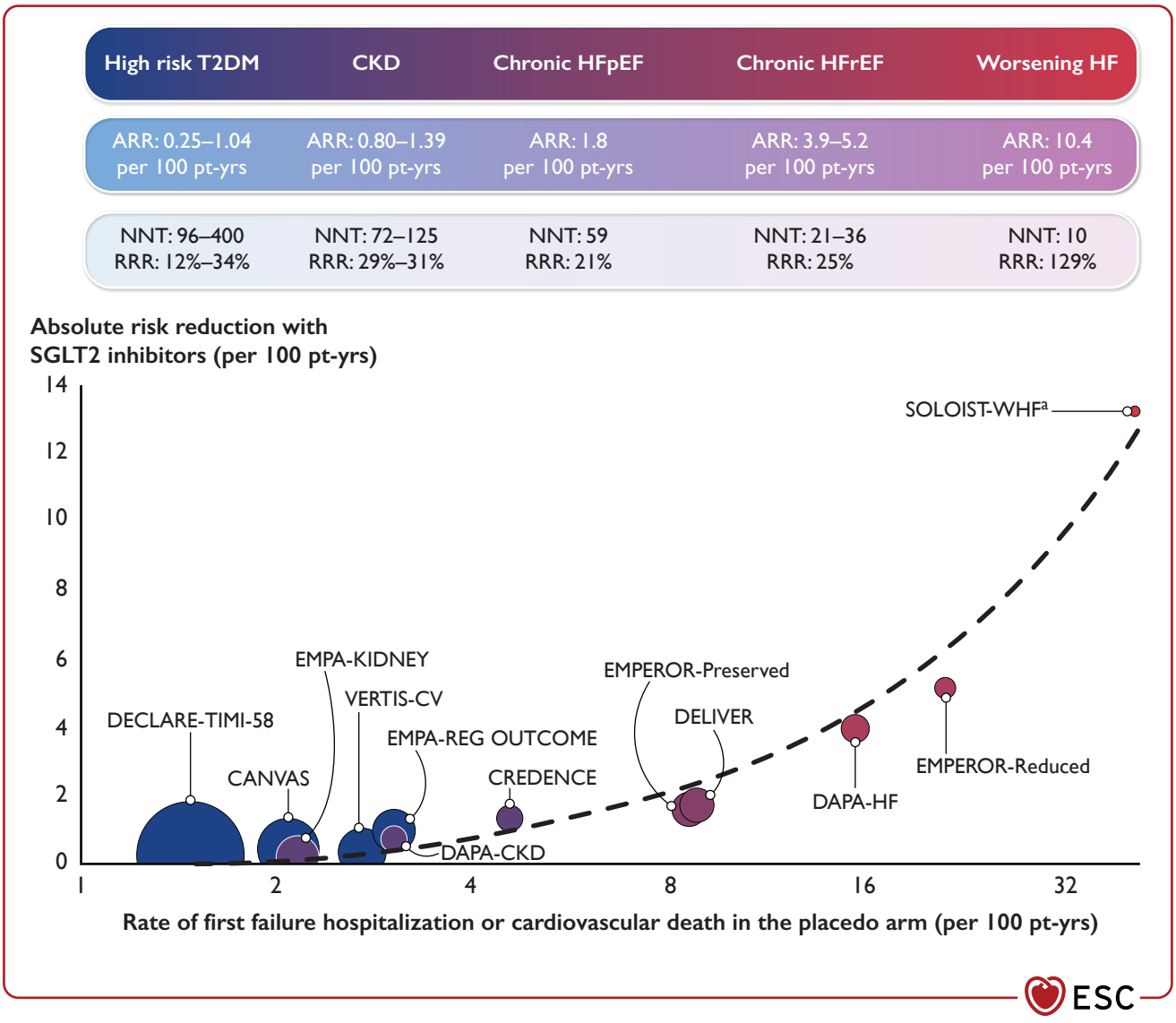

Figure 15 Absolute risk reduction with sodium–glucose co-transporter-2 inhibitors in relation to patient risk based on rate of heart failure-related endpoints in the placebo arm of the respective trials. ARR, absolute risk reduction; CKD, chronic kidney disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NNT, number needed to treat; pt-yrs, patient-years; RRR, relative risk reduction; SGLT2, sodium–glucose co-transporter-2; T2DM, type 2 diabetes mellitus. Bubble plots demonstrate the consistent reductions in time to cardiovascular mortality or first HF hospitalization with SGLT2 inhibitors across all trials, with a greater ARR in patients at higher risk. The size of the bubble represents the sample size of the trial. NNT is estimated from the ARR. [a]Event rates of first HF hospitalization or cardiovascular mortality were not reported in SOLOIST-WHF.[189] Figure adapted from Butler *et al.* 2021.[539]

In addition, four trials investigated the effect of SGLT2 inhibition in patients with CKD: CREDENCE (with canagliflozin) and SCORED (with sotagliflozin) in patients with T2DM; DAPA-CKD (with dapagliflozin) and EMPA-KIDNEY (with empagliflozin) in patients with and without diabetes. In these patients at high risk of HF, a consistent risk reduction of CV death or HF hospitalization was observed ranging from 23% to 31%.[150,153,542,543]

A meta-analysis of six outcome trials of four SGLT2 inhibitors in patients with T2DM (EMPA-REG OUTCOME, CANVAS Programme [two trials], DECLARE-TIMI-58, CREDENCE, VERTIS CV) demonstrated a 32% reduction in HF hospitalization, with no heterogeneity between trials; the effect on HF hospitalization was independent of ASCVD.[155] Thus, SGLT2 inhibitors are recommended for patients with T2DM and multiple ASCVD risk factors or established ASCVD to reduce HF hospitalization.

7.5.2. Glucagon-like peptide-1 receptor agonists

Eight CVOTs have been completed with GLP-1 RAs in patients with T2DM, and the prevalence of established HF in these trials ranged from 9% to 24%. Most GLP-1 RAs had a neutral effect on risk of HF hospitalization in the placebo-controlled RCTs assessing CV safety of glucose-lowering medications in patients with T2DM with or at high risk of ASCVD, despite increasing heart rate by 3–5 b.p.m.[70,72,158–163,544] In addition, two meta-analyses including eight trials comprising 60 080 patients found HF hospitalization to be reduced by 10–11% by GLP-1 RA compared with placebo.[164,545]

The AMPLITUDE-O trial, comparing efpeglenatide with placebo, showed a nominally significant benefit on hospitalization for HF. The trial included stratified randomization by baseline or anticipated use of SGLT2 inhibitors and had the highest prevalence (15.2%) of

SGLT2 inhibitor use among GLP-1 RA trials. Data from an exploratory analysis of the AMPLITUDE-O trial suggest that the efficacy and safety of efpeglenatide was independent of concurrent SGLT2 inhibitor use, including HF hospitalization.[546]

Only three small RCTs of GLP-1 RAs have been conducted in patients with HFrEF.[547] The LIVE trial randomly assigned 241 patients with chronic, stable HFrEF with or without DM to placebo or liraglutide.[548] While no changes in LVEF, quality of life, or functional class were noted after 24 weeks of treatment, more serious adverse cardiac events (sustained ventricular tachycardia, AF requiring intervention, and aggravation of IHD; 12 [10%] vs. 3 [3%] for liraglutide and placebo, respectively; $P = 0.04$) occurred in the liraglutide group. The FIGHT trial (Functional Impact of GLP1 for HF Treatment) randomly assigned 300 patients with and without DM with HFrEF and a recent hospitalization for HF to liraglutide or placebo. Following 180 days of treatment, the primary outcome (time to death, time to re-hospitalization for HF, and time-averaged proportional change in NT-proBNP level from baseline to 180 days) was not different between groups. In addition, there was a non-significant between-group difference in the number of re-hospitalizations for HF (63 [41%] in the liraglutide group vs. 50 [34%] in the placebo group; HR 1.30, 95% CI, 0.89–1.88; $P = 0.17$).[549] The third trial was a small ($n = 82$), randomized study evaluating 12 weeks of albiglutide vs. placebo in patients with HFrEF. No significant differences were seen in LVEF, 6 min walk test, myocardial glucose utilization, or oxygen use.[550] The study was too small and too short to evaluate clinical outcomes.

7.5.3. Dipeptidyl peptidase-4 inhibitors

Four DPP-4 inhibitors (sitagliptin, saxagliptin, alogliptin, and linagliptin) have been examined in dedicated placebo-controlled CV safety trials in patients with T2DM with or at high risk of ASCVD. Saxagliptin significantly increased the risk of HF hospitalization[172] and is not recommended in patients with DM with or at increased risk of HF. Alogliptin was associated with a non-significant trend towards an increase in HF hospitalization.[173] Sitagliptin and linagliptin had a neutral effect.[174,178–180] Vildagliptin, not tested in a CVOT, had no significant effect on LVEF but led to an increase in LV volumes in a small trial.[551]

7.5.4. Insulin

In patients with T2DM and advanced HF, insulin use is independently associated with a significantly worse prognosis.[552] Two basal insulins have been formally evaluated in dedicated CV outcomes trials. In the ORIGIN trial, 12 537 patients (mean age 63.5 years) at high CV risk, with IFG, IGT, or T2DM, were randomized to insulin glargine titrated to a fasting blood glucose level of ≤5.3 mmol/L (≤95 mg/dL) or standard care. After a median follow-up of 6.2 years, insulin glargine was neutral in its effect on HF hospitalizations.[553] The DEVOTE randomized trial, a double-blind comparison of the ultra-long-acting, once-daily insulin degludec vs. insulin glargine U100, enrolled 7637 patients with T2DM with ASCVD or at high CV risk.[181] Treatment with insulin degludec vs. insulin glargine did not differ with respect to HF hospitalization; prior HF was independently associated with future HF hospitalization.[554]

7.5.5. Metformin

Metformin is suggested to be safe at all stages of HF with preserved or stable, moderately reduced kidney function (i.e. eGFR >30 mL/min/1.73 m^2). It is associated with a lower risk of death and HF hospitalization compared with insulin and sulphonylureas in observational studies, though dedicated randomized, controlled, CVOTs evaluating safety and efficacy of metformin have not been conducted.[555–557] Concerns regarding lactic acidosis have not been substantiated.[558,559]

7.5.6. Sulphonylureas

Data on the effects of sulphonylureas on HF are inconsistent. Data from two retrospective cohort studies, including 111 971 patients with diabetes, suggest an adverse safety profile showing ~20–60% higher death rate and ~20–30% higher risk of HF compared with metformin.[560,561] However, in the UKPDS, NAVIGATOR (Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research), and ADOPT trials, there were no increased HF signals.[127,562–564] In addition, data from the CAROLINA trial comparing linagliptin (shown to not increase the risk of HF hospitalization vs. placebo in the CARMELINA trial) vs. glimepiride did not show an elevated risk of HF hospitalization by this sulphonylurea.[179]

7.5.7. Thiazolidinediones

Thiazolidinediones increased the risk of HF hospitalization in several trials and are not recommended in patients with diabetes and symptomatic HF.[165,565–567]

7.5.8. Special consideration: hypoglycaemia and risk of heart failure hospitalization

Although severe hypoglycaemic events were associated with higher HF hospitalization in some but not all studies, there is no clear evidence for causality.[139,140,554,568] Recent analyses have demonstrated bi-directional associations between hypoglycaemia and CV outcomes, including HF, suggesting that this is not causal, but rather reflects underlying frailty and risk of adverse outcomes.[139,140]

Figure 16 summarizes glucose-lowering treatment of patients with HF and T2DM.

Recommendation Table 22 — Recommendations for glucose-lowering medications in patients with type 2 diabetes with and without heart failure

Recommendations	Class[a]	Level[b]
Recommendations for glucose-lowering medications to reduce heart failure hospitalization in patients with type 2 diabetes with or without existing heart failure		
SGLT2 inhibitors (empagliflozin, canagliflozin, dapagliflozin, ertugliflozin, or sotagliflozin[c]) are recommended in patients with T2DM with multiple ASCVD risk factors or established ASCVD to reduce the risk of HF hospitalization.[71,150–153,541]	I	A
SGLT2 inhibitors (dapagliflozin, empagliflozin, or sotagliflozin[c]) are recommended in patients with T2DM and HFrEF to reduce the risk of HF hospitalization and CV death.[189,491,494,497]	I	A
Empagliflozin or dapagliflozin are recommended in patients with T2DM and LVEF >40% (HFmrEF and HFpEF) to reduce the risk of HF hospitalization or CV death.[530,532,533]	I	A
Recommendations for additional glucose-lowering agents with safety demonstrated for heart failure hospitalization in patients with type 2 diabetes if additional glucose control is needed		
GLP-1 RAs (lixisenatide, liraglutide, semaglutide, exenatide ER, dulaglutide, efpeglenatide) have a neutral effect on the risk of HF hospitalization, and should be considered for glucose-lowering treatment in patients with T2DM at risk of or with HF.[70,158–164,545]	IIa	A
DPP-4 inhibitors (sitagliptin and linagliptin) have a neutral effect on the risk of HF hospitalization, and should be considered for glucose-lowering treatment in patients with T2DM at risk of or with HF.[174,179,180]	IIa	A
Basal insulins (glargine and degludec) have a neutral effect on the risk of HF hospitalization and should be considered for glucose-lowering treatment in patients with T2DM at risk of or with HF.[553,554]	IIa	B
Metformin should be considered for glucose-lowering treatment in patients with T2DM and HF.[d,555,556,558]	IIa	B
Recommendations for glucose-lowering medications with an increased risk of heart failure hospitalization in patients with type 2 diabetes		
Pioglitazone is associated with an increased risk of incident HF in patients with diabetes and is not recommended for glucose-lowering treatment in patients at risk of HF (or with previous HF).[165,566]	III	A
The DPP-4 inhibitor saxagliptin is associated with an increased risk of HF hospitalization in patients with diabetes and is not recommended for glucose-lowering treatment in patients at risk of HF (or with previous HF).[172]	III	B
Recommendations for special consideration		
It is recommended to switch glucose-lowering treatment from agents without proven CV benefit or proven safety to agents with proven CV benefit.[e]	I	C

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; ER, extended release; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; s.c., subcutaneous; SGLT2, sodium–glucose co-transporter-2; T2DM, type 2 diabetes mellitus.

[a]Class of recommendation.

[b]Level of evidence.

[c]Sotagliflozin is a dual SGLT1/2 inhibitor.

[d]Chronic and stable HF.

[e]Agents with proven benefit: SGLT2 inhibitors: empagliflozin, canagliflozin, dapagliflozin, sotagliflozin[c]; GLP-1 RAs: liraglutide, semaglutide s.c., dulaglutide, efpeglenatide. In the VERTIS CV trial, ertugliflozin did not reduce the primary endpoint (three-point MACE) nor the key secondary endpoint (CV death or HF hospitalization), but reduced HF hospitalization as a secondary exploratory endpoint.

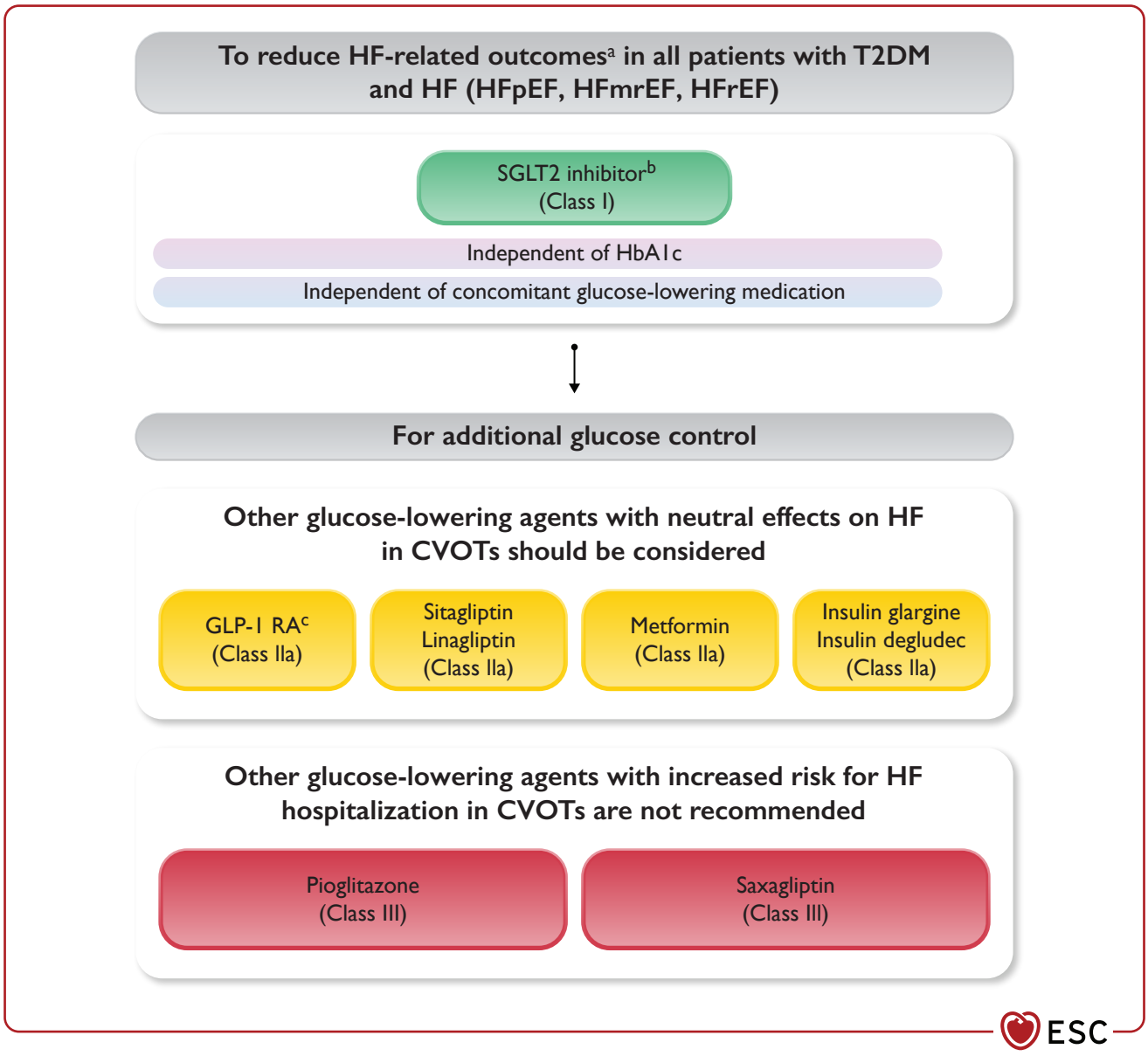

Figure 16 Glucose-lowering treatment of patients with heart failure and type 2 diabetes. CVOT, cardiovascular outcomes trial; DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; Hb1Ac, glycated haemoglobin; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; SGLT2, sodium–glucose co-transporter-2; T2DM, type 2 diabetes mellitus. [a]This includes HF hospitalization or CV death. [b]Empagliflozin, dapagliflozin, or sotagliflozin in patients with HFrEF, empagliflozin or dapagliflozin in patients with HFpEF and HFmrEF. [c]Preferred in patients with atherosclerotic cardiovascular disease and if weight reduction is needed; do not combine with DPP-4 inhibitors.

8. Arrhythmias: atrial fibrillation, ventricular arrhythmias, and sudden cardiac death and diabetes

Diabetes may increase the risk of cardiac arrhythmias via several factors including: associated CV risk factors (e.g. hypertension), CVD (i.e. CAD, prior MI, HF, or stroke), and diabetes-associated factors such as glucose control or diabetic neuropathy.[157,569–572] The risk of cardiac arrhythmias or sudden cardiac death (SCD) in patients with diabetes is most often related to the presence and severity of underlying CVD, but diabetes-related factors may induce arrhythmias independently of CV comorbidities.[157,573–577] The risk of conduction disturbances and need for pacemaker therapy may also be higher in patients with T2DM than in controls, although the general management for these issues should not differ from that for other patients.[578,579]

8.1. Atrial fibrillation and diabetes

8.1.1. Epidemiology of atrial fibrillation and its association with diabetes

Patients with T1DM or T2DM may exhibit atrial electrical and structural remodelling associated with increased vulnerability for AF.[580–583] Many epidemiological studies have reported an association of diabetes (mainly T2DM) with incident AF.[584,585] Recent, large analyses confirmed that T1DM was also independently associated with a higher incidence of AF.[586–588] Diabetes duration has also been associated with AF; each year with diabetes conferred a 3% increase in the risk of AF.[589] A meta-analysis of 11 studies with 108 703 AF cases in 1 686 097 patients showed a 40% greater risk of AF in the presence of diabetes. The effect was attenuated but still significant after adjusting for other risk factors (RR 1.24; 95% CI, 1.06–1.44).[590] Although men have higher absolute rates for incidence of AF, the relative rates of incident AF associated with diabetes are higher in women than in men for both T1DM and T2DM.[586–588]

Diabetes and AF frequently co-exist, and when this occurs, there is a substantially higher risk of all-cause death, CV death, stroke, kidney disease, and HF, regardless of diabetes type.[541,577,591–596] Risk factors commonly associated with diabetes and AF (and not fully dissociable, e.g. hypertension and obesity) are also likely to worsen prognosis. In several observational studies, the age-adjusted association of diabetes with incident AF was no longer significant after multiple adjustments for hypertension, CV comorbidity, BMI, or obesity, thus suggesting that strategies for preventing AF in patients with diabetes should focus on controlling diabetes-associated comorbidities (especially weight, sleep apnoea, and BP).[597–600]

Intensive glucose lowering (target HbA1c <6.0%) has been associated with similar incident AF rates than a less-stringent approach (HbA1c <8.0%).[601] The rate of new-onset AF may, however, be affected by diabetes therapy.[577] The impact of anti-hyperglycaemic agents on the risk of AF is still debated. It has been suggested that metformin and pioglitazone may reduce the risk of AF.[602] SGLT2 inhibitors, compared with placebo, were associated with more new-onset AF cases in EMPA-REG OUTCOME (empagliflozin vs. placebo), but fewer incident AF cases in CANVAS (canagliflozin vs. placebo) and DECLARE-TIMI 58 (dapagliflozin vs. placebo).[71,151,153,603] In the EMPA-REG OUTCOME trial, empagliflozin, compared with placebo, reduced CV death or HF hospitalization consistently in patients with diabetes with or without AF ($P_{int} = 0.56$).[604] It has recently been reported that finerenone may reduce new-onset AF in patients with T2DM and CKD.[605] This is consistent with results obtained with other MRAs in HF.[508,606]

In the ADVANCE study, patients with diabetes and AF (~8%) had higher risks of all-cause death, CV death, major cerebrovascular events, and HF compared with patients with diabetes without AF. Lowering BP resulted in similar RR reduction in all-cause and CV death but, due to their higher risk of these events, the absolute benefits from BP control was much greater in patients with AF.[607] In the VALUE (Valsartan Antihypertensive Long-term Use Evaluation) trial, hypertensive patients with new-onset diabetes had higher rates of new-onset AF compared with patients without diabetes, and were at a higher risk of HF.[608] Hence, AF in patients with diabetes should be viewed as a marker of adverse outcome, which should prompt aggressive management of all concomitant risk factors.[609]

8.1.2. Screening and managing atrial fibrillation in patients with diabetes

Detecting AF in patients with diabetes has clinical consequences because the risk of stroke is markedly higher in these patients. In the absence of other comorbidities, the annual risk of stroke can be estimated at 2.2% per year in isolated diabetes.[610] Since asymptomatic (silent) AF is not uncommon, patients with diabetes should be opportunistically screened for AF by palpating pulse or by ECG.[611] Patients with diabetes at high risk of AF would likely benefit from an active screening for AF, but more data are needed to define optimal AF screening strategies also including modern equipment, such as wearable digital devices in patients with diabetes (Supplementary data online, *Table S16*).[612,613] Before starting treatment, clinical AF should

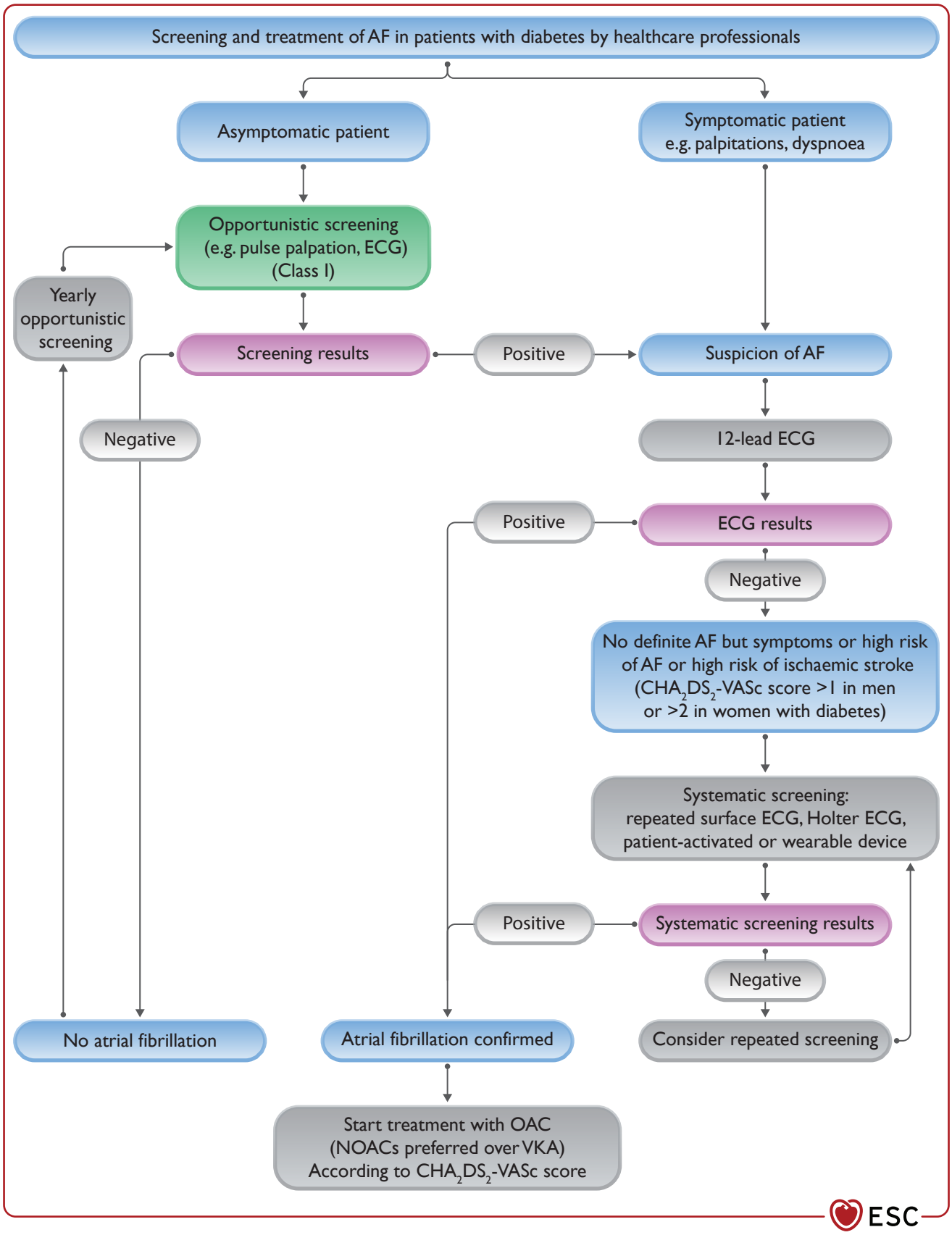

Figure 17 Screening for atrial fibrillation in patients with diabetes. AF, atrial fibrillation; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes mellitus, Stroke or transient ischaemic attack (2 points), Vascular disease, Age 65–74 years, Sex category (female); ECG, electrocardiogram; OAC, oral anticoagulant; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist.

be well documented using surface-lead ECG (≥30 s showing heart rhythm with no discernible repeating P waves and irregular R–R intervals when atrioventricular conduction is not impaired; *Figure 17*).[600,614]

In patients with diabetes and established AF, controlling the ventricular rate is recommended to decrease symptoms and prevent AF-related complications, while asymptomatic patients mainly need thromboembolic prevention. In those with persistent symptoms despite adequate rate control, or in those with LV dysfunction attributable to poorly controlled high ventricular rate, rhythm-control strategies should be attempted, including cardioversion, antiarrhythmic drug use, and catheter ablation, which is the general management in this setting whether diabetes is present or not.[600,615–617] For details on managing AF, please refer to the 2020 ESC/EACTS Guidelines for the diagnosis and management of atrial fibrillation and recent European Heart Rhythm Association scientific documents.[577,600,613]

8.1.3. Preventing stroke in patients with atrial fibrillation and diabetes

Stratifying AF stroke risk with diabetes should use the established CHA_2DS_2-VASc (Congestive HF, Hypertension, Age ≥75 years [2 points], Diabetes mellitus, Stroke/transient ischaemic attack [2 points], Vascular disease, Age [65–74 years], Sex category [female]) score; following stratification, stroke prevention (i.e. OAC) should be started in patients with >1 risk factor.[600,618] The score is likely higher in patients with diabetes due to the common association with other risk factors for stroke, such as arterial hypertension, age over 65 or 75 years, associated vascular disease, or HF. Several studies found that diabetes independently predicted stroke in patients with AF.[619] However, diabetes may not be a significant risk factor for stroke in the elderly.[620] The Stroke in AF Working Group attributed a RR of 1.7 (95% CI, 1.4–2.0) for stroke in patients with AF and diabetes, as well as an absolute stroke risk of 2–3.5% per year for non-anticoagulated patients in the same population.[621] Diabetes is probably not the most potent independent risk factor for stroke in AF compared with the other items in the CHA_2DS_2-VASc score, but it is included in this risk-stratification tool, giving a point alongside most other items.[600,618,622–624] The increased risk of stroke associated with AF and diabetes is similar in T1DM and T2DM except perhaps a slightly increased risk in T2DM compared with T1DM in patients <65 years of age. The risk of stroke in patients with diabetes and AF may increase with longer diabetes duration, increasing levels of HbA1c, and more diabetes-related comorbidities, such as nephropathy and retinopathy.[625,626]

As an OAC is being initiated, a clinical bleeding risk score, such as the HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly [>65 years], Drugs/alcohol concomitantly) score, should be used to identify patients at risk of bleeding, and importantly, to address the potentially reversible bleeding risk factors (that should be considered in all patients, irrespective of HAS-BLED score).[600] Due to the increased risk of several CV adverse events in patients with diabetes, a similar RR reduction with OACs generally translates into greater ARR in the diabetes population.[577] The beneficial efficacy and safety of NOACs compared with warfarin seem conserved in patients with AF and diabetes, irrespective of their baseline stroke risk or the presence of other CV risk factors.[577,627–629]

Recommendation Table 23 — Recommendations for atrial fibrillation in patients with diabetes

Recommendations	Class[a]	Level[b]
Screening		
Opportunistic screening for AF by pulse taking or ECG is recommended in patients ≥65 years of age.[577,611,630,631]	I	B
Opportunistic screening for AF by pulse taking or ECG is recommended in patients with diabetes <65 years of age (particularly when other risk factors are present) because patients with diabetes exhibit a higher AF frequency at a younger age.[577,611,631,632]	I	C
Systematic ECG screening should be considered to detect AF in patients aged ≥75 years, or those at high risk of stroke.[577,633–635]	IIa	B
Anticoagulation		
Oral anticoagulation is recommended for preventing stroke in patients with AF and diabetes and with at least one additional (CHA_2DS_2-VASc) risk factor for stroke.[636]	I	A
For preventing stroke in AF, NOACs are recommended in preference to VKAs, with the exception of patients with mechanical valve prostheses or moderate to severe mitral stenosis.[637]	I	A
Oral anticoagulation should be considered for preventing stroke in patients with AF and diabetes but no other CHA_2DS_2-VASc risk factor for stroke. This includes patients with T1DM or T2DM <65 years old.[638–640]	IIa	B
Use of a formal, structured, bleeding risk score (HAS-BLED score) should be considered to identify modifiable and non-modifiable risk factors for bleeding in patients with diabetes and AF, and to identify patients in need of closer follow-up.[641–643]	IIa	B

AF, atrial fibrillation; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥ 75 years (2 points), Diabetes mellitus, Stroke or transient ischaemic attack (2 points), Vascular disease, Age 65–74 years, Sex category (female); ECG, electrocardiogram; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly; NOAC, non-vitamin K antagonist oral anticoagulant; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; VKA, vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.

8.2. Ventricular arrhythmias and risk of sudden cardiac death and diabetes

Compared with the general population, patients with diabetes have an increased risk of both SCD and non-SCD.[575,615,644–646] In a meta-analysis of 14 studies involving 346 356 participants and 5647 SCD cases, the risk of SCD was two-fold higher in patients with diabetes compared with patients without diabetes (adjusted HR 2.25; 95% CI, 1.70–2.97).[647] However, patients with diabetes also exhibited a nearly three-fold greater risk of non-SCD than patients without

diabetes (adjusted HR 2.90; 95% CI, 1.89–4.46).[646] Men at all ages have a higher risk of SCD than women, but in the presence of diabetes, the risk of SCD is higher in both men and women.[575,615,644–646,648]

Both hyperglycaemia and hypoglycaemia are independently associated with increased risk of ventricular arrhythmias.[649] Insulin-induced hypoglycaemia has been associated with nocturnal death (also called 'dead-in-bed syndrome') in T1DM, and arrhythmic deaths were reported in several T2DM trials.[187,576,650–654] Diabetic kidney disease might also play a role in the arrhythmia-associated mechanism of sudden death in this setting.[655]

Hypoglycaemia-associated arrhythmias are difficult to document, but observational studies using CGM and Holter monitoring in small T2DM cohorts showed that hypoglycaemic episodes were common, often asymptomatic, and associated with various arrhythmias.[656,657] Compared with daytime hypoglycaemia, nocturnal episodes were more common and associated with a greater risk of bradycardia or atrial ectopy, while ventricular arrhythmias were equally common.[656,657]

The use of antiarrhythmic drugs should follow the general principles and precautions related to pharmacological treatment of cardiac arrhythmias.[600,658] In patients with diabetes and an ICD, there is an increased risk of death in those who have appropriate therapy compared to those who do not.[659] In contrast, patients with diabetes may have a lower risk of inappropriate therapy or ICD shock, since they may be more sedentary with consequently less frequent exercise-induced sinus tachycardia and also lower incidence of lead fracture.[600,658,659]

Observational studies have reported significant corrected QT (QTc) interval prolongation possibly associated with microvascular complications, atypical patterns of microvolt T-wave alternans, altered heart rate variability, or heart rate turbulence in patients with diabetes, but none of these tests should routinely be used to stratify the risk of ventricular arrhythmias or SCD in clinical practice.[658,660–668] There may also be a direct effect of both hyper- and hypoglycaemia on QTc interval.[669–671] The mechanisms by which hyperglycaemia may produce ventricular instability may be increased sympathetic activity, increased cytosolic calcium content in myocytes, or both.[672] The risk of cardiac events is usually related to the underlying heart disease rather than ventricular premature beats.[669–671]

There is no diabetes-specific protocol for SCD screening, but all patients diagnosed with diabetes should undergo regular evaluation for CV risk factors or structural heart disease.[48,576,658] Patients with diabetes and symptoms suggestive of cardiac arrhythmias (e.g. palpitations, pre-syncope, or syncope) should undergo further detailed diagnostic assessment.[576] Patients with diabetes and frequent premature ventricular beats, episodes of non-sustained ventricular tachycardia, or symptoms suggestive of HF should be examined for the presence of an underlying structural heart disease and their eligibility for an ICD should be assessed; this is a general principle in managing patients with HF, irrespective of diabetes status.[658] In case of sustained ventricular arrhythmias, diagnosing underlying structural heart disease with imaging techniques and coronary angiography is usually needed if no obvious trigger factors, such as electrolyte imbalance, can be identified.[48,576,658]

Although cardiac arrhythmias were not specifically investigated in either the LEADER or the EMPA-REG OUTCOME trials, an antiarrhythmic effect of these drugs (perhaps mediated by glucagon-release stimulation or increased blood ketone bodies, which may have sympathico-suppressive effects) has been hypothesized to contribute to the reduced risk of CV death.[71,72] In the DAPA-HF trial, dapagliflozin reduced the risk of the composite outcome of serious ventricular arrhythmia, resuscitated cardiac arrest, or sudden death by 21% in patients with HFrEF, compared with placebo.[673] The benefit was mainly observed >9 months post-randomization, suggesting that the beneficial effects of dapagliflozin require time to develop and may involve cellular mechanisms that slow the progression of HFrEF.[674] However, a recent meta-analysis indicated that SGLT2 inhibition was not associated with an overall lower risk of SCD or ventricular arrhythmias in patients with T2DM and/or HF and/or CKD, although the point estimates suggested potential benefits.[675]

9. Chronic kidney disease and diabetes

9.1. Chronic kidney disease definitions, staging, and screening

Chronic kidney disease has a major effect on global morbidity and mortality.[676] CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health. It is staged primarily by categories of glomerular filtration rate (GFR) and albuminuria.[677] The CKD Epidemiology Collaboration (CKD-EPI) has developed accurate eGFR equations based on creatinine ± cystatin C measurements.[678] An eGFR ≥60 mL/min/1.73 m^2 does not constitute CKD unless there is albuminuria or other evidence of kidney disease (*Table 11*).[677] A persistent decrease in eGFR <60 mL/min/1.73 m^2 (i.e. stages G3–5), however, is sufficient to confirm CKD. This level of eGFR is associated with increased risk of CKD progression and CVD.[43,679,680] The most advanced stage of CKD is characterized by an eGFR <15 mL/min/1.73 m^2, and recently implemented nomenclature refers to this as 'kidney failure'.[681] Such low levels of eGFR may

Table 11 KDIGO staging by glomerular filtration rate and urinary albumin-to-creatinine ratio categories with colour chart for risk of initiation of maintenance kidney replacement therapy

	Albuminuria stage		
eGFR stage (mL/min/ 1.73 m^2)	**A1 <3 mg/ mmol (<30 mg/g)**	**A2 3–30 mg/mmol (30–300 mg/g)**	**A3 >30 mg/ mmol (>300 mg/g)**
G1 (≥90)			
G2 (60–89)			
G3a (45–59)			
G3b (30–44)			
G4 (15–29)			
G5 (<15)			

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.
Note that this staging uses a ratio 1:10 to convert the urinary albumin-to-creatinine ratio from mg/mmol to mg/g, but the precise ratio is 1:8.84.
Green is low risk (and represents no CKD if there is no structural or histological evidence of kidney disease). Relative to low risk (estimated at 0.04/1000 patient-years), yellow is moderately increased risk (at least ~5×), orange is high risk (at least ~20×), and red is very high risk (at least ~150×). Risk of cardiovascular death approximately mirrors the same pattern.
Table adapted from the KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Reprinted with permission from Elsevier.[677]

necessitate the need to start maintenance kidney replacement therapy (KRT).[677]

Albuminuria is an early marker of nephropathy and predicts both risk of kidney failure and CVD independently of eGFR.[43,682] Nephropathy caused by diabetes is a leading cause of CKD globally, and screening patients with diabetes for CKD is recommended at least annually.[676,677] A spot urine sample measuring UACR is an efficient method to identify and quantify albuminuria.[677,683] Changes in UACR or GFR slope are used as surrogate trial endpoints for nephroprotection, but more definitive evidence for reducing risk of kidney failure in patients with diabetes generally requires categorical endpoints based on a ≥40% sustained decline in GFR.[684,685]

9.2. Management of cardiovascular disease risk and kidney failure in patients with chronic kidney disease and diabetes

Risk of CVD increases progressively with lower levels of eGFR and, in those with advanced CKD, structural abnormalities of the heart, HF, and sudden death are particular features.[679,680,686–688] Increased risk of CAD also accompanies CKD, often with calcification of atherosclerotic plaques.[679,689] Accelerated vascular media calcification with increased vascular stiffness is also a feature of CKD and attributed to disordered calcium–phosphate metabolism, referred to as CKD-mineral bone disorder (CKD-MBD).[690,691] Managing CVD risk in patients with CKD and diabetes may, therefore, need to consider multiple interventions and both traditional and CKD-specific risk factors.[361,692–694]

All patients with diabetes and CKD should be offered standard advice on smoking, nutrition, and exercise.[45] A raised BMI is independently associated with risk of CKD, and behavioural interventions to promote weight loss in people with T2DM reduce the risk of developing very high-risk CKD over the long-term.[57,695,696] Management of people with diabetes and CKD is then based on sequentially initiating and titrating doses of pharmacological interventions with proven efficacy (*Figure 18*).

Statin-based therapy reduces the risk of major atherosclerotic events (i.e. coronary death, non-fatal MI, ischaemic stroke, and coronary revascularization) in patients with CKD, but does not meaningfully slow progression of CKD.[248,697–699] Trials of statin-based therapy, combined in collaborative meta-analyses, show a trend towards smaller relative reductions per mmol/L reduction in LDL-C on major atherosclerotic events as eGFR declines, with uncertainty about benefits among patients on dialysis.[697] This diminution in RR reduction at decreased eGFR implies that more intensive LDL-C-lowering regimens are required to maximize benefits.[697] The goal in patients with CKD and diabetes should be to achieve the largest possible absolute reduction in LDL-C safely.[697,700]

Four large trials recruiting different types of patients with CKD have confirmed the safety of intensive LDL-C lowering with statins alone (atorvastatin, rosuvastatin, fluvastatin), or combining a moderate dose of simvastatin with ezetimibe.[698,701–704] Although there is no dedicated, large-scale trial of a PCSK9 inhibitor in patients with CKD, sub-group analyses by CKD stage from the FOURIER trial of the PCSK9 inhibitor evolocumab found its LDL-C-lowering effect was preserved in patients with stage G3 CKD, and CV benefits on atherosclerotic events appeared unmodified by baseline eGFR.[699]

Several drugs developed to manage CVD risk or hyperglycaemia have been shown to reduce the risk of CKD progression in large trials that recruited patients with T2DM and CKD (*Figure 18*). These include RAS inhibitors, SGLT2 inhibitors, and finerenone. There is increasing evidence that these interventions should be started early to prevent end-organ damage in at-risk patients.

Blocking RAS with an ACE-I (captopril) or ARBs (irbesartan/losartan) prevented kidney failure in patients with diabetes and overt nephropathy in dedicated clinical outcomes trials.[705–707] ARBs (irbesartan/telmisartan) also slowed progression from microalbuminuria (albuminuria stage A2) to overt nephropathy.[708,709] These RAS inhibitors are therefore recommended in patients with diabetes as soon as CKD is clinically diagnosed. Combining an ARB with an ACE-I, however, is not recommended, as large trials have identified an increased risk of hyperkalaemia and acute kidney injury, without demonstrable additional benefits of such 'dual-blockade' on risk of kidney failure or CVD.[710]

In contrast, combining an SGLT2 inhibitor with an ACE-I or ARB has clear beneficial effects on risk of kidney failure and hospitalization for HF in patients with CKD and T2DM.[153,542] The CREDENCE, DAPA-CKD, and EMPA-KIDNEY placebo-controlled trials were all stopped early for efficacy while testing canagliflozin, dapagliflozin, and empagliflozin, respectively.[153,543,711] All three trials found the RR reductions for kidney disease progression were unmodified by baseline eGFR, with EMPA-KIDNEY reporting clear benefits in patients with eGFR 20–30 mL/min/1.73 m^2.[153,542,543,712,713] EMPA-KIDNEY included 254 patients with an eGFR <20 mL/min/1.73 m^2 at randomization, and once initiated, SGLT2 inhibitors could be continued until the need of KRT. As patients with decreased eGFR are at the highest absolute risk of kidney disease progression, these trials' results should encourage the initiation of SGLT2 inhibitors in patients with CKD down to at least an eGFR of 20 mL/min/1.73 m^2 with continued use until the need for KRT (despite low eGFR substantially attenuating their HbA1c-lowering effect). Meta-analysis of all the large SGLT2 inhibitor trials shows benefits of SGLT2 inhibitors on the risk of HF hospitalization or CV death are also unmodified by eGFR (at a trial level; *Figure 19*).[714] The combined SGLT1/2 inhibitor sotagliflozin was analysed vs. placebo in the SCORED trial in patients with T2DM and CKD (eGFR 25–60 mL/min/1.73 m^2); sotagliflozin reduced the primary composite of the total number of CV deaths, hospitalizations for HF, and urgent visits for HF by 26% vs. placebo (HR 0.74; 95% CI, 0.63–0.88; $P < 0.001$).[150] Initiating an SGLT2 inhibitor alongside an ACE-I or ARB is therefore recommended in patients with T2DM following the first clinical evidence of CKD. In patients with T1DM and CKD, the absence of large trials with sufficient follow-up means it is unclear whether the absolute benefits of SGLT2 inhibitors on kidney failure and CVD outcomes are outweighed by the high absolute risk of ketoacidosis with SGLT2 inhibitors.[715,716]

MRAs reduce BP and albuminuria in patients with CKD.[717] The placebo-controlled FIDELIO-DKD (Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease) and FIGARO-DKD (Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease) trials demonstrated for the non-steroidal MRA finerenone that these effects translate into reduced risk of kidney failure and a reduction of the combined CV outcome of CV death, non-fatal MI, non-fatal stroke, or hospitalization for HF in patients with CKD and T2DM who are already on maximum ACE-I or ARB.[718–720] FIDELIO-DKD demonstrated reduced risk of a categorical kidney outcome, a primary composite outcome combining kidney failure, a sustained decline in eGFR of at least 40%, or death from renal causes, in patients with eGFR 25–60 mL/min/1.73 m^2 and UACR of 34–567 mg/mmol (30–5000 mg/g), or eGFR 60–75 mL/min/1.73 m^2 with UACR of 34–567 mg/mmol (300–5000 mg/g; mean eGFR 43 ± 13 mL/min/1.73 m^2; median UACR 96 mg/mmol [852 mg/g]).[719]

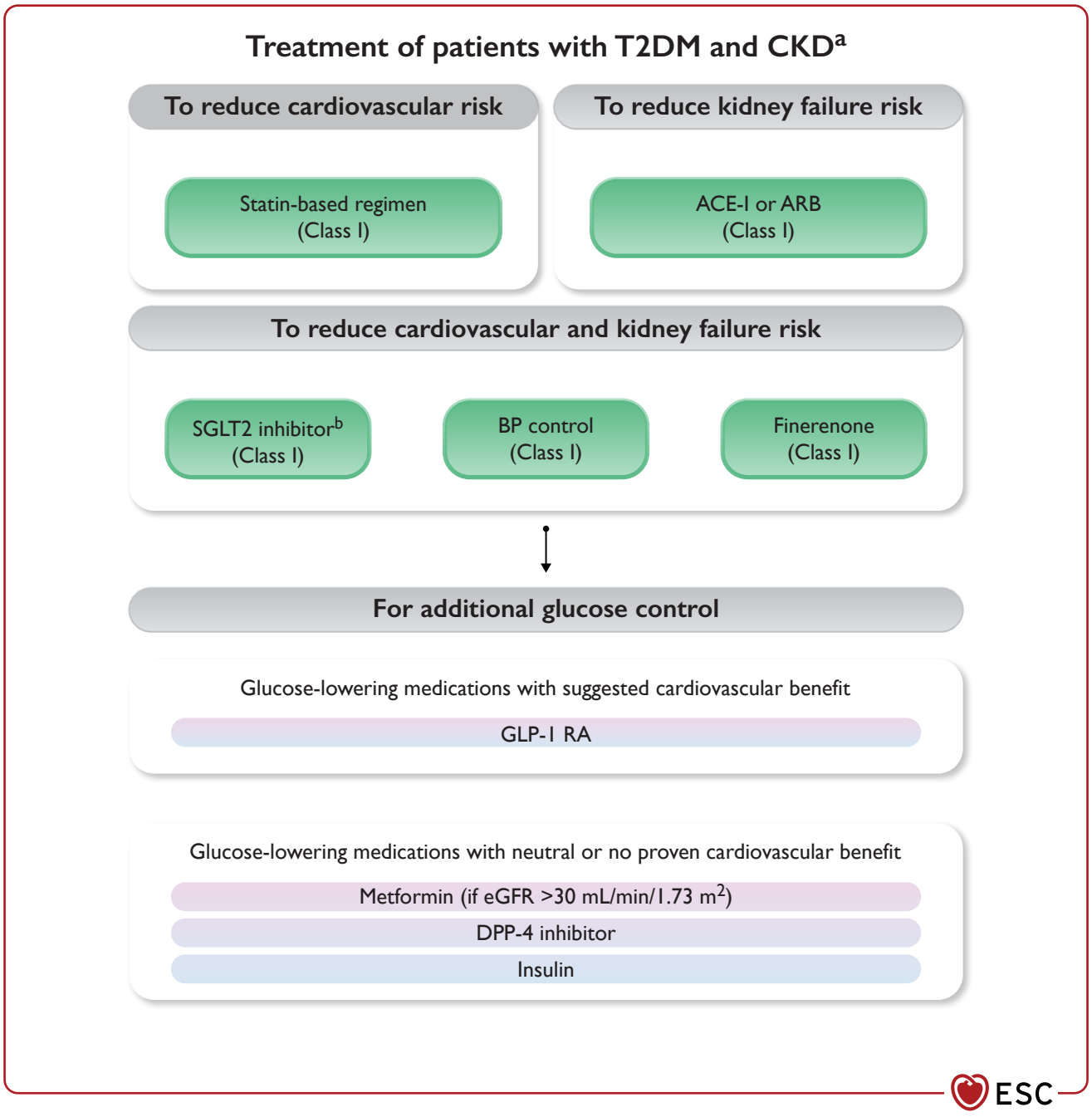

Figure 18 Pharmacological management to reduce cardiovascular or kidney failure risk in patients with type 2 diabetes and chronic kidney disease. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; RAS, renin–angiotensin system; SGLT2, sodium–glucose co-transporter-2; T2DM, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio. [a]A statin-based regimen reduces CV risk in CKD while ACE-I or ARBs reduce kidney failure risk; SGLT2 inhibitors, BP control, and finerenone reduce both CV risk and kidney failure risk. SGLT2 inhibitors, RAS inhibitors, and finerenone are particularly effective at reducing risk of kidney failure when albuminuria is present [e.g. UACR ≥3 mg/mmol (30 mg/g); stage A2 and A3]. [b]Canagliflozin, empagliflozin, or dapagliflozin.

Information on the safety and efficacy of combining MRAs with SGLT2 inhibitors in CKD is limited as only ∼4% of FIDELIO-DKD, ∼8% of FIGARO-DKD, ∼5% of DAPA-CKD, and no CREDENCE participants were prescribed such a combination.[153,718,719,721] Sub-group analyses considering those co-prescribed MRA and SGLT2 inhibitors suggest their combined use does not modify safety findings from the key trials.[150,189,722–726]

FIDELIO-DKD and FIGARO-DKD excluded patients with a potassium of >4.8 mmol/L, as MRAs cause hyperkalaemia.[718,719] Combining RAS and SGLT2 inhibitors does not appear to cause hyperkalaemia, and a hypothesis has been raised that SGLT2 inhibitors reduce the risk of severe hyperkalaemia among MRA users with HF.[153,542,710,723,724,727,728] Finerenone is therefore recommended in addition to an RAS inhibitor in patients with T2DM and eGFR

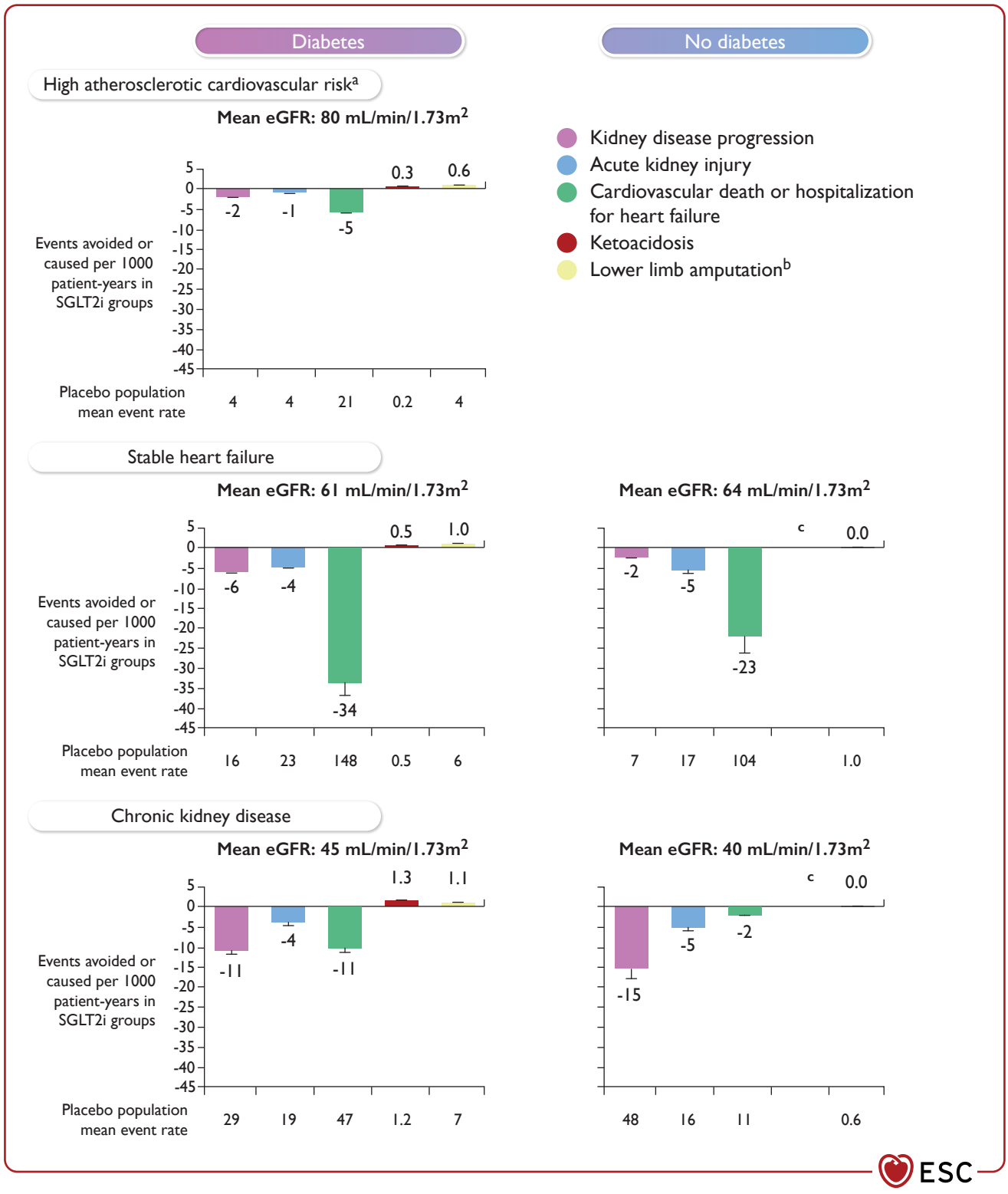

Figure 19 Absolute benefits and harms of sodium–glucose co-transporter-2 inhibitors in patients with and without diabetes. eGFR, estimated glomerular filtration rate; RR, relative risk; SE, standard error; SGLT2i, sodium–glucose co-transporter-2 inhibitor. Patient group-specific absolute effects estimated by applying the diabetes sub-group-specific RR to the average event rate in the placebo arms (first event only). Negative numbers indicate events avoided by SGLT2 inhibition per 1000 patient-years. Error bars represent SE in the numbers of events avoided or caused, estimated from uncertainty in the RRs. Mean eGFR values are given for combined trial populations by patient group and diabetes status. Placebo population mean event rates are the absolute numbers of events per 1000 patient-years in the placebo groups of all trials in the relevant subpopulation. [a]Additionally, two (SE 0.5) fewer myocardial infarctions per 1000 patient-years of SGLT2i treatment were observed in the diabetes and high atherosclerotic cardiovascular risk group. [b]RRs to determine absolute effects for lower-limb amputation included the CANVAS trial. [c]Too few ketoacidosis events to estimate absolute effects. Figure adapted from the Nuffield Department of Population Health Renal Studies Group and SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. This is an open access article distributed under the terms of the Creative Commons CC-BY License. https://creativecommons.org/licenses/by/4.0/[714]

>60 mL/min/1.73 m^2 with UACR ≥34 mg/mmol (≥300 mg/g), or eGFR 25–60 mL/min/1.73 m^2 and UACR ≥3 mg/mmol (≥30 mg/g), with appropriate potassium monitoring.[718,719]

9.3. Blood pressure and glycaemic control in patients with diabetes and chronic kidney disease

In patients with T2DM, BP lowering reduces CV risk, with relative benefits similar in people with and without CKD.[196,693,729] RR reductions for CVD per 10 mmHg of lower SBP are greater in patients with a starting SBP of ≥140 mmHg, but a reduced risk of stroke and albuminuria is evident with a further reduction in SBP in those with an SBP <140 mmHg.[196] Whether intensively lowering moderately elevated SBP prevents kidney failure, however, is uncertain.

The effect of tight glycaemic control, as compared with standard control, on risk of kidney failure is also uncertain, but such an approach reduces risk of developing or worsening of diabetic nephropathy based on measures of albuminuria.[132,133,730] Personalized HbA1c targets of 6.5–8.0% (48–64 mmol/mol) are suggested for people with diabetes and CKD, with a target <7.0% (<53 mmol/mol) still recommended to reduce microvascular complications, wherever possible.[132,133] Above eGFR 30 mL/min/1.73 m^2, metformin with appropriate dose adjustment can be used, but below eGFR 30 mL/min/1.73 m^2, metformin should generally be stopped to avoid risk of lactic acidosis due to its accumulation.[731,732]

In CKD, HbA1c monitoring may be less reliable when eGFR is <30 mL/min/1.73 m^2, and self-monitoring or CGM may help safely achieve tight glycaemic control in such patients.[45]

Another potential strategy to help achieve glycaemic targets in patients with CKD is use of GLP-1 RAs. Extrapolating evidence from trials in patients with T2DM suggest GLP-1 RAs safely improve glycaemic control and may reduce weight and CV risk in patients with CKD.[164] Meta-analysis of the GLP-1 RAs trials (lixisenatide, liraglutide, semaglutide, exenatide, albiglutide, dulaglutide, efpeglenatide) showed they favourably lower levels of albuminuria in T2DM, with some GLP-1 RAs reducing MACE in those with prior CVD or at high CV risk.[164] The size of RR reductions on MACE appears similar in people with or without reduced eGFR.[164] Dulaglutide has been tested in patients with T2DM and CKD stages G3–4. It was as effective at lowering HbA1c as insulin glargine, but it reduced weight, had lower rates of symptomatic hypoglycaemia, and slowed eGFR decline compared with insulin glargine.[733] The benefits of GLP-1 RAs on risk of kidney failure have yet to be confirmed, and a definitive assessment of semaglutide in the FLOW (Effect of Semaglutide Versus Placebo on the Progression of Renal Impairment in Subjects With Type 2 Diabetes and Chronic Kidney Disease) trial of 3535 patients with T2DM and albuminuric CKD is ongoing.[734]

An alternative to GLP-1 RAs in CKD is a DPP-4 inhibitor. Linagliptin safely lowers HbA1c in patients with T2DM and CKD but does not reduce risk of CVD or kidney failure.[180]

9.4. Roles for antithrombotic therapy and invasive strategies in managing atherosclerotic cardiovascular disease in patients with diabetes and chronic kidney disease

Low-dose ASA (75–100 mg o.d.) is indicated in patients with diabetes and/or CKD and ASCVD.[325] In primary ASCVD prevention in T2DM and CKD, the benefits and risks of low-dose ASA may be finely counterbalanced.[291,292,325,735] CKD is associated with both increased ASCVD and bleeding risk, and so the net effects of low-dose ASA (75 mg o.d.) in CKD (stages G3–G4 or G1–2 with albuminuria) without ASCVD is being tested in the large, open-label, ATTACK (Aspirin to Target Arterial Events in Chronic Kidney Disease) trial.[679,736,737] The net benefit of low-dose rivaroxaban (2.5 mg b.i.d.) on atherothrombotic vs. bleeding risk is also being tested in the large, placebo-controlled, TRACK (Treatment of Cardiovascular Disease with Low Dose Rivaroxaban in Advanced Chronic Kidney Disease) trial in people with CKD stage G4–5 who are at high CVD risk due to diabetes, age >65 years, or prior ASCVD.[738]

Invasive vs. medical management strategies for stable moderate or severe CAD in CKD have been assessed in the ISCHEMIA-CKD (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches–Chronic Kidney Disease) trial, in which 57% (444/777) of participants had diabetes.[739] The trial was conducted in parallel with the large ISCHEMIA trial.[740] When results from both these trials are considered alongside one another, ISCHEMIA-CKD suggests that an initial conservative approach using intensive medical therapies to manage stable CAD is appropriate for patients with diabetes and an eGFR <30 mL/min/1.73 m^2.[739] ISCHEMIA-CKD did not replicate the anti-anginal benefits of an invasive strategy observed in ISCHEMIA, but such benefits should not be ruled out due to lower power.[739,740] It should also be noted that patients with acute MI, unstable CAD, or unacceptable levels of angina were excluded from both trials, meaning optimal management of such conditions in patients with CKD may still include an intensive strategy (*Section 6*).

Serum phosphate may increase in advanced CKD (e.g. eGFR <30 mL/min/1.73 m^2) and is associated with an increased risk of CVD.[694] Lowering phosphate, controlling parathyroid hormone, and maintaining normal calcium levels is common practice in nephrology despite a lack of definitive evidence that it modifies risk of CVD.[691,741] Some evidence suggests the dose of calcium-based phosphate binders should be restricted.[742,743] In patients with T2DM and CKD, correcting renal anaemia improves quality of life, but does not reduce the risk of CVD and may increase the risk of stroke.[744] Renal specialist advice should be sought for managing a raised serum phosphate (>1.5 mmol/L) or other evidence of CKD-MBD, and renal anaemia (e.g. haemoglobin <10 g/dL).

Recommendation Table 24 — Recommendations for patients with chronic kidney disease and diabetes

Recommendations	Class[a]	Level[b]
Intensive LDL-C lowering with statins or a statin/ezetimibe combination is recommended.[c,697,698]	I	A
A BP target of ≤130/80 mmHg is recommended to reduce risk of CVD and albuminuria.[196]	I	A
Personalized HbA1c targets 6.5–8.0% (48–64 mmol/mol) are recommended, with a target <7.0% (<53 mmol/mol) to reduce microvascular complications, wherever possible.[132,133]	I	A
The maximum tolerated dose of an ACE-I or ARB is recommended.[705–709]	I	A
A SGLT2 inhibitor (canagliflozin, empagliflozin, or dapagliflozin)[d] is recommended in patients with T2DM and CKD with an eGFR ≥20 mL/min/1.73 m^2 to reduce the risk of CVD and kidney failure.[150,153,542,543,711,714,715]	I	A

Continued

Finerenone is recommended in addition to an ACE-I or ARB in patients with T2DM and eGFR >60 mL/min/1.73 m^2 with a UACR ≥30 mg/mmol (≥300 mg/g), or eGFR 25–60 mL/min/1.73 m^2 and UACR ≥3 mg/mmol (≥30 mg/g) to reduce CV events and kidney failure.[718–720]	I	A
A GLP-1 RA is recommended at eGFR >15 mL/min/1.73 m^2 to achieve adequate glycaemic control, due to low risk of hypoglycaemia and beneficial effects on weight, CV risk, and albuminuria.[164]	I	A
Low-dose ASA (75–100 mg o.d.) is recommended in patients with CKD and ASCVD.[325,735]	I	A
It is recommended that patients with diabetes are routinely screened for kidney disease by assessing eGFR defined by CKD-EPI and UACR.[43,678,745]	I	B
Treatment with intensive medical or an initial invasive strategy is recommended in people with CKD, diabetes, and stable moderate or severe CAD, due to similar outcomes.[e,740,746]	I	B
Kidney specialist advice may be considered for managing a raised serum phosphate, other evidence of CKD-MBD, and renal anaemia.	IIb	C
Combined use of an ARB with an ACE-I is not recommended.[710]	III	B

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; ASA, acetylsalicylic acid; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CAD, coronary artery disease; CKD, chronic kidney disease; CKD-EPI, chronic kidney disease epidemiology; CKD-MBD, chronic kidney-mineral bone disorder; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; LDL-C, low-density lipoprotein-cholesterol; o.d., once daily; SGLT2, sodium–glucose co-transporter-2; T2DM, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio.

[a]Class of recommendation.

[b]Level of evidence.

[c]Little evidence of benefit in patients on dialysis.

[d]Sotagliflozin reduces CV risk but has not demonstrated a reduction in the risk of kidney failure.

[e]ISCHEMIA-CKD trial primary and key secondary outcomes were a composite of 'death or non-fatal myocardial infarction' and 'death, non-fatal myocardial infarction, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest', respectively.

10. Aortic and peripheral arterial diseases and diabetes

10.1. The impact of diabetes on peripheral atherosclerosis

Diabetes is one of the most important risk factors for the development and progression of atherosclerosis.[747–751] The number of patients with atherosclerosis associated with diabetes is steadily increasing alongside the increasing number of patients with diabetes worldwide. Peripheral atherosclerosis summarizes LEAD and carotid atherosclerosis.

10.1.1. Diabetes and lower-extremity artery disease

The impact of diabetes differs between vascular territories.[747] The strong correlation between LEAD and diabetes is well established.[747–749] Up to 30% of all patients with intermittent claudication and ~50–70% of patients with chronic limb-threatening ischaemia (CLTI) have diabetes.[750,752] Patients with diabetes and LEAD show specific anatomic and morphologic characteristics, which are important for further management.[753] In addition, patients with diabetes have occlusions of arteries below the knee more often than do patients without diabetes. Moreover, severe calcification, such as media sclerosis and development of collateral circulation, is typical for these patients.[753]

Compared with patients without diabetes, those with diabetes develop LEAD at a younger age and have faster LEAD progression, with more patients having CLTI. Prolonged diabetes duration, suboptimal glycaemic control, co-existing CV risk factors, and other end-organ damage (e.g. proteinuria) increase the prevalence of LEAD.[751] Moreover, patients with microangiopathy are at increased risk of CLTI and major amputation.[754,755] In a cohort study with 125 674 participants, the presence of microvascular disease such as retinopathy, nephropathy, or neuropathy independently increased the risk of amputation.[754]

For patients with a diabetic foot ulcer (diabetic foot disease), the risk of death at 5 years is 2.5 times higher than for patients with diabetes but no foot ulcer.[752,756] In patients with diabetes, pain is often masked because of peripheral neuropathy with decreased pain sensitivity. Therefore, atherosclerosis is often advanced when diagnosed. CLTI is the clinical presentation of advanced disease, characterized by ischaemic rest pain; however, pain may be absent in patients with diabetes. The 2017 ESC Guidelines on the diagnosis and treatment of peripheral arterial diseases and the 2019 Global Vascular Guidelines on the management of chronic limb-threatening ischaemia proposed the Wound, Ischaemia, and foot Infection (WIfI) classification to stratify amputation risk and the potential benefits of revascularization (Supplementary data online, *Table S17*).[747,757,758] Patients with diabetes and critical limb ischaemia are at very high risk of lower-limb amputation and recurrent wounds. All of these factors increase the risk of limb infection.

Although 20–30% of patients with diabetes have LEAD, more than half of these have no clinical symptoms.[760] Therefore, screening and early diagnosis is important to allow early treatment and prevent major amputation. Clinical evaluation includes medical history, assessing symptoms, palpating peripheral pulses, and evaluating skin colour and temperature. In addition, examination for neuropathy is important; however, the sensitivity of clinical examination is limited.[761] Therefore, screening for LEAD is indicated in patients with diabetes and foot ulceration.[747,761] There is a lack of evidence concerning the frequency of screening for LEAD in patients with diabetes, but it seems plausible to assess leg perfusion regularly.

An ankle–brachial index (ABI) ≤0.90 is diagnostic for LEAD, with 80% sensitivity and 95% specificity in all populations.[760,762] However, the accuracy of ABI is lower in patients with diabetes.[762,763] Beyond LEAD, an ABI ≤0.90 (or >1.40) is associated with an increased risk of death and CV events.[762,763] Measuring ABI can be difficult due to medial calcinosis (ABI >1.40), in which case, other tests are useful for diagnosing LEAD, including Doppler waveform analysis of the ankle arteries, or the toe–brachial index (TBI), which may be helpful because medial calcinosis barely affects digital arteries. A TBI <0.70 is diagnostic for LEAD.[747,763]

In patients with intermittent claudication, a treadmill test is useful for assessing walking distance.[747] Duplex scan is the first-line imaging for confirming LEAD and should be performed at least when revascularization is indicated. Magnetic resonance angiography or CT angiography can also help to plan further treatment (*Figure 20*).

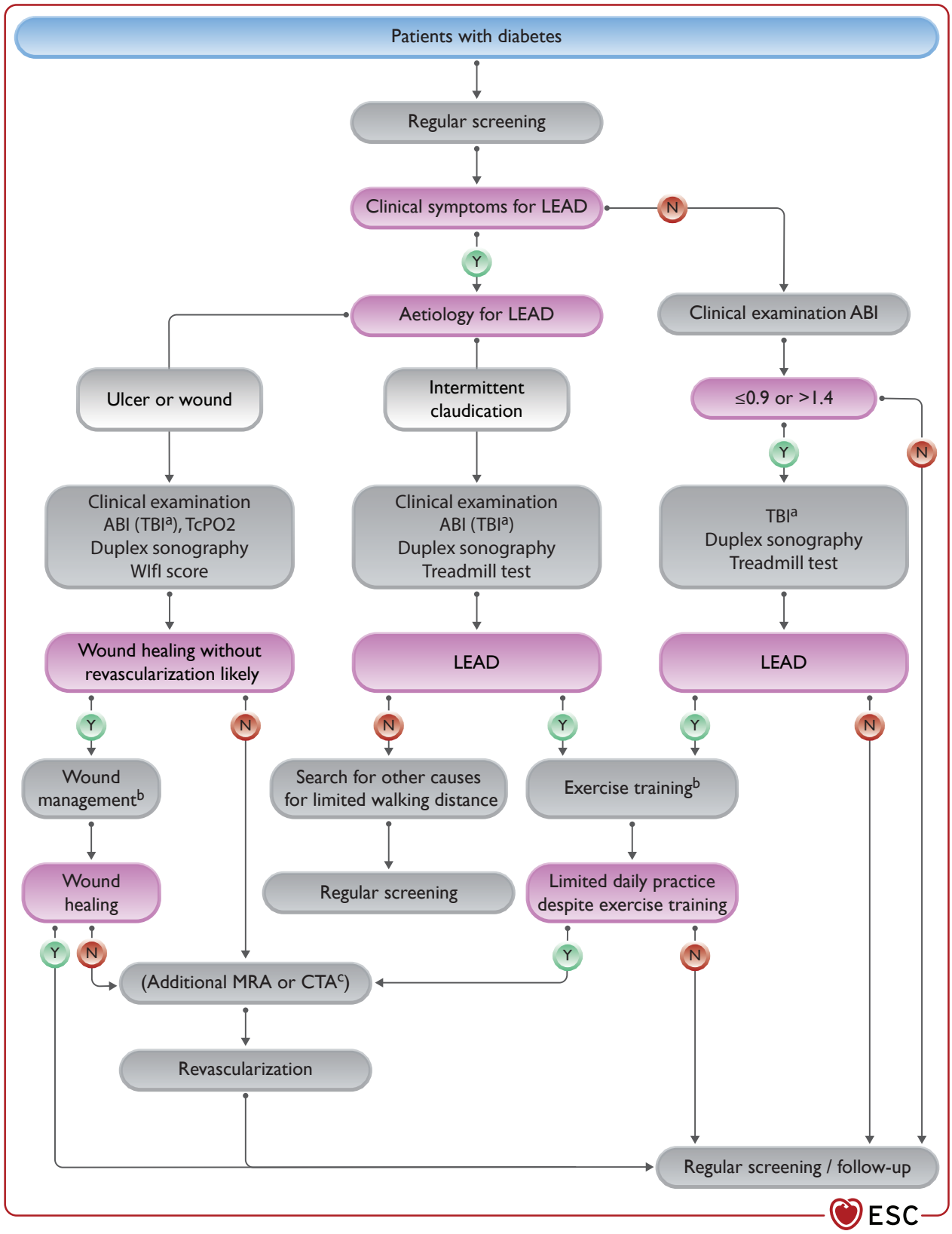

Figure 20 Screening for and managing lower-extremity artery disease in patients with diabetes. ABI, ankle–brachial index; CTA, computed tomography angiography; LEAD, lower-extremity artery disease; MRA, magnet resonance angiography; TBI, toe–brachial index; $TcPO_2$, transcutaneous oxygen pressure; WIfI, Wound, Ischaemia, foot Infection. [a]TBI when ABI >1.4. [b]Further information regarding wound management and exercise training can be found in the 2017 ESC Guidelines on the diagnosis and treatment of peripheral arterial diseases.[747] [c]MRA or CTA when duplex sonography is not sufficient for planning revascularization.

Due to the high burden of comorbidities in patients with diabetes, interdisciplinary co-operation is crucial. The medical management of LEAD in patients with diabetes does not differ from that recommended for patients with ASCVD in general including SGLT2 inhibitors and GLP-1 RAs.[747,757,764,765] Still, it should be noted that for the SGLT2 inhibitor canagliflozin, the risk of amputation was increased in the CANVAS study, a finding that has not been repeated in the CREDENCE trial comparing canagliflozin with placebo in patients with T2DM and CKD, nor in CVOTs with other SGLT2 inhibitors.[151] Still, according to US Food and Drug Administration requirements, the amputation risk with canagliflozin is described in the Warnings and Precautions section of the prescribing information. There are some discussions as to whether the use of GLP-1 RAs could be preferable in patients with LEAD. Ongoing studies may help to clarify this question in the future.

Recent data showed that the combination of low-dose ASA and rivaroxaban 2.5 mg b.i.d. reduces MACE and major adverse limb events including amputation (MALE) compared with ASA and placebo, particularly in patients with PAD.[766] A sub-group analysis of patients with LEAD showed a significantly higher MACE and MALE rate compared with patients with CAD and a higher benefit of the combination therapy.[767] Improvement of prognosis was similar in patients with (44%) and without diabetes. The total number of major bleeding events was increased but fatal or critical organ bleeding did not.

Patients with intermittent claudication should take part in exercise training programmes (30–45 min, at least three times per week), as regular intensive exercise improves walking distance.[747]

In patients with CLTI, revascularization must be attempted when possible, and amputation should only be considered when revascularization options fail.[768] With respect to the revascularization modality of choice, we refer to dedicated guidelines. There has not been a specific trial on revascularization strategies in patients with diabetes; however, a review of 56 studies including patients with diabetes suggested higher limb-salvage rates after revascularization (78–85% at 1 year) compared with conservative management.[768] Due to disease progression, long-term follow-up is very important in patients with diabetes and LEAD.[769]

10.1.2. Diabetes and carotid artery disease

According to the results of a recent community-based study, the prevalence of diabetes linearly correlated with carotid plaques, and patients with diabetes had more advanced carotid atherosclerosis than individuals without diabetes.[770] Based on a prospective cohort study with 300 patients, which showed a high prevalence of carotid atherosclerosis especially in men, screening of male patients with diabetes and a history of CAD or ABI <0.85 has been suggested.[771] Nevertheless, in patients with diabetes without a history of cerebrovascular disease, there is only limited evidence that carotid screening improves outcomes, and regular screening is not recommended.[747,772] Asymptomatic carotid artery disease is frequently treated conservatively, and the patient is followed up with duplex ultrasound.

Carotid revascularization should be considered in asymptomatic patients with one or more indicators of increased stroke risk (previous transient ischaemic attack/stroke, ipsilateral silent infarction, stenosis progression, or high-risk plaques), and if the estimated peri-operative stroke or death rate is <3% and the patient's life expectancy is >5 years. In symptomatic patients, carotid revascularization is indicated if the stenosis is >70%, and should be considered if the stenosis is >50%, assuming that the estimated peri-operative stroke or death rate is <6%.[747]

With respect to the impact of diabetes on carotid revascularization, a meta-analysis of 14 observational studies involving 16 264 patients showed that patients with diabetes had a higher risk of peri-operative stroke and death versus those without diabetes.[773] The CREST (Carotid Revascularization Endarterectomy versus Stenting) trial was the only trial comparing carotid endarterectomy and carotid artery stenting to enrol enough patients with diabetes ($n = 759$) for sub-group analysis.[774] Although re-stenosis rates were low at 2 years after carotid stenting (6.0%) and carotid endarterectomy (6.3%), diabetes predicted re-stenosis with both techniques.

Details on revascularization strategies can be found in the 2017 ESC Guidelines on the diagnosis and treatment of peripheral arterial diseases.[747]

10.2. Diabetes and aortic aneurysm

Current evidence shows a lower risk of developing aortic aneurysm in patients with diabetes compared with persons without diabetes.[759,775,776] There are different mechanisms under discussion including effects on extracellular matrix volume, extracellular matrix glycation, the formation of advanced glycation end-products, inflammation, oxidative stress, and intraluminal thrombus biology.[777] Moreover, some medications, such as metformin used to treat diabetes, seem to have protective effects on the development of abdominal aortic aneurysms.

Nevertheless, aortic aneurysm is associated with atherosclerosis and general secondary prevention is recommended based on expert consensus.

Recommendation Table 25 — Recommendations for peripheral arterial and aortic diseases in patients with diabetes

Recommendation	Class[a]	Level[b]
Lower-extremity arterial disease		
In patients with diabetes and symptomatic LEAD, antiplatelet therapy is recommended.[325]	I	A
In patients with diabetes and CLTI, it is recommended to assess the risk of amputation; the WIfI score is useful for this purpose.[747,758]	I	B
As patients with diabetes and LEAD are at very high CV risk, a LDL-C target of <1.4 mmol/L (<55 mg/dL) and a LDL-C reduction of at least 50% is recommended.[778,779]	I	B
Screening for LEAD is recommended on a regular basis, with clinical assessment and/or ABI measurement.	I	C
Patient education about foot care is recommended in patients with diabetes, and especially those with LEAD, even if asymptomatic. Early recognition of tissue loss and/or infection, and referral to a multidisciplinary team, is mandatory to improve limb salvage.	I	C
An ABI ≤0.90 is diagnostic of LEAD, irrespective of symptoms. In symptomatic cases, further assessment including duplex ultrasound is recommended.	I	C
When ABI is elevated (>1.40), other non-invasive tests, including TBI or duplex ultrasound, are recommended.	I	C

Continued

Duplex ultrasound is recommended as the first-line imaging method to assess the anatomy and haemodynamic status of lower-extremity arteries.	I	C
In case of CLTI, revascularization is recommended whenever feasible for limb salvage.[747,758]	I	C
In patients with chronic, symptomatic LEAD without high bleeding risk, a combination of low-dose rivaroxaban (2.5 mg b.i.d.) and ASA (100 mg o.d.) should be considered.[766]	IIa	B
Carotid artery disease		
In patients with diabetes and carotid artery disease, it is recommended to implement the same diagnostic work-up and therapeutic strategies (medical, surgical, or endovascular) as in patients without diabetes.	I	C
Aortic aneurysm		
In patients with diabetes and aortic aneurysm, it is recommended to implement the same diagnostic work-up and therapeutic strategies (medical, surgical, or endovascular) as in patients without diabetes.	I	C

ABI, ankle–brachial index; ASA, acetylsalicylic acid; b.i.d., twice a day; CLTI, chronic limb-threatening ischaemia; CV, cardiovascular; LDL-C, low-density lipoprotein-cholesterol; LEAD, lower-extremity artery disease; o.d., once a day; TBI, toe–brachial index; WIfI, Wound, Ischaemia, foot Infection.
[a]Class of recommendation.
[b]Level of evidence.

11. Type 1 diabetes and cardiovascular disease

This section summarizes evidence-based recommendations to effectively manage CV risk factors in patients with T1DM; the section does not address the control of glucose levels, which must follow the principles of patient self-management under the guidance of the diabetes healthcare multidisciplinary team according to clinical recommendations by EASD/ADA.[1]

People with T1DM face a three-fold increase in mortality compared with the general population, which translates into an 11-year reduction in life expectancy; CVD mortality accounts for 30–44% of all deaths in patients with T1DM.[780–784]

The DCCT prospectively investigated not only the impact of an intensified glucose-lowering treatment strategy on microvascular complications in patients with T1DM, but also the rate of macrovascular events at long-term follow-up. This study showed that intensified insulin therapy lasting over a mean of 6.5 years halved the incidence and progression of microvascular sequelae, which was associated with a significant decrease in HbA1c, compared with conventional therapy.[126] After a mean follow-up of 17 years in >90% of the initially enrolled patients, CV risk was also significantly reduced by 42% in the intensified-treatment group, and the reduction in HbA1c over the first 6.5 years was significantly associated with a reduction in CV risk.[785] In the EDIC (Epidemiology of Diabetes Interventions and Complications) study, patients were followed up for over 30 years and the following was concluded: (i) hyperglycaemia is the primary modifiable mediator of late complications in T1DM; (ii) near-normal glucose control reduces the incidence and progression of microvascular complications, such as retinopathy, nephropathy, and neuropathy; and (iii) intensive diabetes therapy reduces CV complications in T1DM.[786]

Recently, a mediation analysis and multi-variable models of the EDIC trial showed that the quality of adjustment of traditional risk factors accounts for only ~50% of the cardio-protective effect of improved metabolic control.[787] About 40% of the cardio-protective effect remains for HbA1c or elevated glucose concentrations per se. Accordingly, recent analyses from the Swedish National Diabetes Register evaluated the prognostic significance of 17 risk factors for death, acute MI, or stroke. Of the 32 611 patients with T1DM in this Swedish registry cohort, 5.5% died over the course of 10.4 years. The strongest predictors of death and CV endpoints were HbA1c, albuminuria, diabetes duration, systolic BP, and LDL-C concentration.[788]

Thus, reducing CV risk in patients with T1DM relates to both lowering HbA1c and controlling other classical CV risk factors, including BP and LDL-C. Therefore, glucose control target values are recommended for most adults with T1DM by the joint consensus report of the ADA and EASD: HbA1c <53 mmol/mol or <7.0%; pre-prandial glucose 4.4–7.2 mmol/L or 80–130 mg/dL; and 1–2 h post-prandial glucose <10.0 mmol/L or <180 mg/dL.[13] Hypoglycaemia should be avoided, especially in patients with CV complications.

Advances in diabetes technologies have started a new era in clinical practice, and the use of CGM has now become widespread. CGM can significantly improve glycaemic control in T1DM, providing more detailed information and introducing new outcome variables including time-in-range and glycaemic variability.[138]

Management strategies should adapt new therapies and technologies as they become available, according to the wishes and desires of the person with diabetes.

11.1. Cardiovascular risk assessment in type 1 diabetes

With respect to treatment targets and thresholds for other CV risk factors, a critical question is predicting CV risk in patients with T1DM without CVD. Determining ASCVD risk in patients with T1DM is less well studied than in patients with T2DM.

In 2011, an observational study using the data from 3661 patients in the Swedish National Diabetes Register proposed a 5-year CVD risk model for use in patients with T1DM.[789] More recently, the Steno Type 1 Risk Engine was externally validated at 5 years but lacks validation at 10 years.[790] Age at the onset and duration of diabetes are two risk factors that lead the estimation of CV risk. Thus, patients diagnosed with T1DM at an early age show an increased incidence of CVD. In addition, excess mortality in patients diagnosed with T1DM under the age of 10 years, compared with those aged 26–30 years at diagnosis, has been highlighted by a Swedish study.[791] This concept has been underlined by the Pittsburgh Epidemiology of Diabetes Complications (EDC) study, which showed duration of diabetes to be an independent risk factor for MACE.[791,792] Several other risk factors related to diabetes management, including glycaemic control, insulin requirements, smoking, cardiac autonomic neuropathy, dysfunctional immune response, and insulin resistance, are to be taken into account.[788]

A recent risk tool, developed based on the Scottish/Swedish Diabetes Registry and validated in the Swedish National Diabetes Register can provide individualized risk predictions.[793] This 10-year ASCVD risk prediction tool https://diabepi.shinyapps.io/cvdrisk/ could facilitate risk estimation and discussions with patients with T1DM.

11.2. Managing cardiovascular risk

Analogies of recommendations for risk-factor modifications in patients with T1DM derive from the fact that there is no direct evidence that CV risk reduction by lowering causal CV risk factors, like LDL-C or

BP, differs in patients with T1DM or T2DM. However, the recommendations are given in the awareness that, in most CVOTs for lipids, BP, antiplatelet agents, and anticoagulation, patients with T1DM were excluded or recruited in small groups. In the following, we summarize recommendations of the respective sections with focus on specific aspects or caveats that should be considered in patients with T1DM.[794]

11.2.1. Exercise and lifestyle

Data on the effects of exercise on T1DM are inconclusive. Aerobic fitness improved HbA1c in patients with T1DM, but did not affect BMI, BP, and lipids.[795]

11.2.2. Lipid lowering

Statins remain the cornerstone of lipid-lowering treatment. In patients with T1DM at a younger age, starting statins early might be justified with long duration of disease, two additional risk factors, or microalbuminuria. In the Cholesterol Treatment Trialists' Collaboration meta-analysis, 1466 patients with T1DM were also included.[248] Increased cholesterol absorption in T1DM compared with T2DM may explain why ezetimibe, a drug that directly decreases cholesterol absorption, may reduce LDL-C more in T1DM than in T2DM.[796,797]

11.2.3. Blood pressure

People with T1DM may benefit from stringent BP-lowering strategies. A recent analysis of the EDC study in patients without known CAD showed that the optimal BP threshold associated with reduced CVD risk was 120/80 mmHg in young adults with childhood-onset T1DM.[798] Routine ambulatory BP monitoring is recommended to identify subjects with masked hypertension, as demonstrated in a Finnish study in which one-quarter of patients with T1DM had underlying hypertension and increased arterial stiffness.[799]

11.2.4. Antiplatelet therapy

Antiplatelet agents may be beneficial in individuals with T1DM without symptomatic ASCVD who have at least one additional major CV risk factor.[800]

11.3. Glucose-lowering agents beyond insulin

Glucagon-like peptide-1 receptor agonists or SGLT2 inhibitors are currently not indicated for T1DM.

Although GLP-1 RAs and SGLT2 inhibitors reduce CV risk in patients with T2DM in large CVOTs, no such data are available for patients with T1DM. For GLP-1 RAs, despite showing potential in reducing HbA1c and weight in patients with T1DM in the ADJUNCT ONE (The Efficacy and Safety of Liraglutide as Adjunct Therapy to Insulin in the Treatment of Type 1 Diabetes) Treat-To-Target trial, concerns have been raised about increased rates of symptomatic hypoglycaemia and hyperglycaemia with ketosis.[801] Another RCT in patients with T1DM also showed no significant overall reduction in HbA1c by liraglutide compared with placebo.[802] Adding SGLT2 inhibitors at a lower than usual dose to insulin therapy in T1DM may reduce glucose variability and facilitate glucose control, thereby reducing insulin doses and hypoglycaemia.[803] However, ketoacidosis at lower glucose levels, so called 'euglycaemic ketoacidosis', has been reported in 2–3% of patients with T1DM taking SGLT2 inhibitors.[804] This is a potentially lethal complication.

11.4. Renal protection in type 1 diabetes

As in patients with T2DM, patients with T1DM should be regularly screened for kidney disease by assessing eGFR defined by CKD-EPI and UACR.[677] RAS blockade with an ACE-I prevents kidney failure in patients with T1DM and overt nephropathy (*Section 9*).[705,805] RAS inhibitors are therefore recommended in patients with T1DM as soon as kidney damage is first clinically evident.

Recommendation Table 26 — Recommendations for patients with type 1 diabetes

Recommendation	Class[a]	Level[b]
In patients with T1DM, it is recommended that adjustment of glucose-lowering medication follows principles of patient self-management under the guidance of the diabetes healthcare multidisciplinary team.	I	C
Avoiding hypoglycaemic episodes is recommended, particularly in those with established CVD.[780–782]	I	C
Statins should be considered for LDL-C lowering in adults older than 40 years with T1DM without a history of CVD to reduce CV risk.[787]	IIa	B
Statins should be considered for use in adults younger than 40 years with T1DM and other risk factors of CVD or microvascular end-organ damage or 10-year CVD risk ≥10% to reduce CVD risk.[787,788]	IIa	B
The use of the Scottish/Swedish risk prediction model may be considered to estimate 10-year CVD risk in patients with T1DM.[793]	IIb	B

CV, cardiovascular; CVD, cardiovascular disease; LDL-C, low-density lipoprotein-cholesterol; T1DM, type 1 diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.

12. Person-centred care

A person-centred approach that encourages and empowers patients to actively take part in finding solutions to their problems is suggested.[806] Person-centred care, including shared decision-making, goes beyond maintaining active person consent to decisions and the person's participation to the development of the therapeutic plan. It shapes disease management to advance the life and health-related quality of life of the person.[806,807] It helps people make better healthcare decisions based on their informed preferences in collaboration with their healthcare professionals (HCPs). [806] Person-centred care requires:

- Identifying and integrating patient needs, background, and culture into decisions regarding health practices.[808–812]
- Active person participation as a key factor for successful self-management.[808] This encompasses all kinds of preferences, as well as physical, psychosocial, behavioural, and financial needs in the development of the therapeutic plan.[808,813] It also refers to meal planning, planned physical activity, managing symptoms, blood glucose monitoring, medical treatments, and managing episodes of illness and of low and high blood glucose, as well as psychosocial, cultural, and spiritual consequences of health conditions.[814–816]

- Motivation and support of people with diabetes, such as: support to stop smoking; adopt a healthy diet; increase PA and exercise; manage other comorbidities, such as arthritis, renal failure, frailty, and cognitive impairment, which increase risk of drug interactions; and manage body weight, taking psychosocial factors into account.[817–826]
- Interdisciplinary teams comprising the person (including caregivers/family), physicians, nurses, social workers, physiotherapists, occupational therapists, dieticians, pharmacists, physical activity specialists, and psychologists are effective for enhancing effective communication, collaboration, and preventing CVD.[827,828] The most effective models of preventive care are those that adopt a total risk-management approach (i.e. those that address all of the risk factors that impact CV health) using behavioural counselling with action plans, education, comprehensive, goal-setting, and problem-solving approaches, and proven therapeutics supported by frequent follow-up, either face to face or by telephone and/or digital health interventions.[820,829,830]

Figure 21 summarizes the model of person-centred care approach for patients with diabetes with or without CVD, considering sex and cultural and socioeconomic factors.

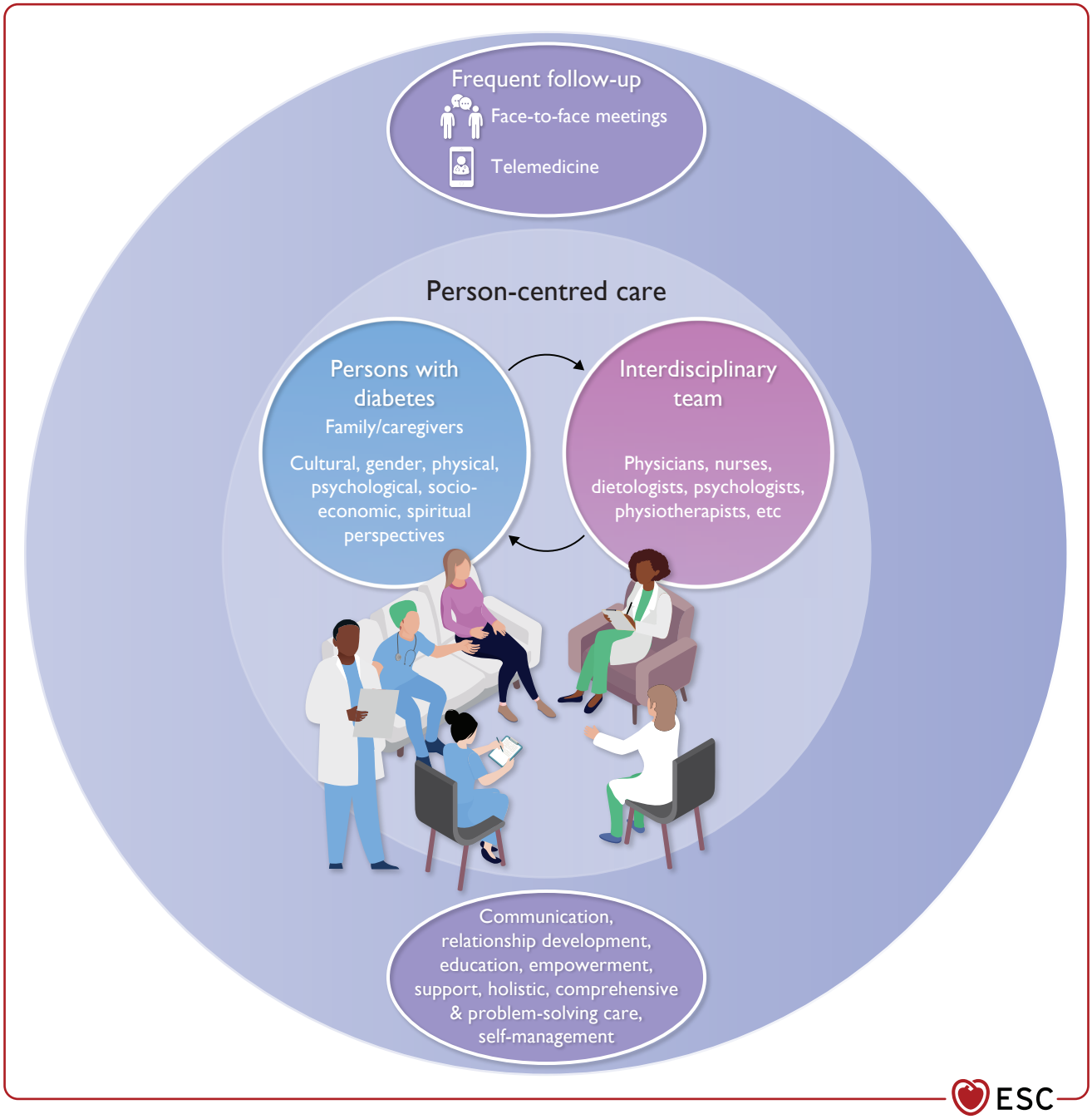

Figure 21 Person-centred care approach for patients with diabetes with or without cardiovascular disease.

Recommendation Table 27 — Recommendations for person-centred care in diabetes

Recommendations	Class[a]	Level[b]
Structured education programmes are recommended in patients with diabetes to improve diabetes knowledge, glycaemic control, disease management, and patient empowerment.[811,812,821]	I	A
Person-centred care is recommended to facilitate shared control and decision-making within the context of person priorities and goals.[822–824]	I	C
Providing individual empowerment strategies should be considered to enhance self-efficacy, self-care, and motivation in patients with diabetes.[825,826,831–834]	IIa	B

[a]Class of recommendation.
[b]Level of evidence.

13. Practical guidance

New guidelines and clinical recommendations for treating T2DM are patient centred and evidence based; the clinical picture and risk of cardio-renal complications, rather than HbA1c alone, are the forefront of personalized treatment decisions. The primary therapeutic goals in patients with diabetes and ASCVD or increased risk of CV complications is protecting organs and improving prognosis (*Figure 1*). Accordingly, these ESC Guidelines on CVD and diabetes are based on the extensive data from large CVOTs of recent years. For patients with T2DM and ASCVD, a wealth of data exists but CV risk reduction in those without ASCVD is less clear. Thus, to provide recommendations for treatment strategies to lower CV risk in patients with T2DM but without ASCVD or severe TOD, an appropriate tool for stratifying risk in these patients is of major importance. Therefore, an extension of SCORE2 for T2DM, named SCORE2-Diabetes, is provided to predict 10-year risk of fatal and non-fatal CVD events (MI, stroke) across four European risk regions in patients without ASCVD or severe TOD.[63]

Implementation of the current Guidelines should be fostered not only by using respective educational tools developed by the ESC including the ESC Clinical Practice Guideline, but also by integrating it into national electronic health-record systems and digital-based healthcare solutions.

The evidence-based concept of the current Guidelines, its key messages, and gaps of evidence as medical needs for future research must be distributed to all healthcare stakeholders, policymakers, politicians, and the general public. Awareness should be raised, respectively, on national and European levels, including in European Union (EU) parliament and responsible commissions.

From our point of view, the current Guidelines might provide a blueprint for approaching multimorbid patients with common, chronic, non-communicable diseases such as ASCVD, HF, diabetes, and CKD. Non-communicable diseases are one of the greatest burdens on healthcare systems and societies in Europe and many other areas of the world. Therefore, we hope that the current Guidelines will contribute to the ultimate goal of managing CVD and CV risk in patients with diabetes: to improve patients' prognosis and health-related quality of life.

14. Key messages

Diagnosis of diabetes

- Raised fasting or random glucose, elevated HbA1c, or an abnormal OGTT is diagnostic of diabetes; a single abnormal test is sufficient with symptoms, while two abnormal tests are usually required without symptoms.
- Undiagnosed diabetes is common, particularly in individuals with CVD. Therefore, screening for diabetes in all individuals with CVD, including HF, is recommended using HbA1c and/or fasting glucose.

Cardiovascular risk assessment

- All patients with diabetes should be evaluated for the presence of ASCVD and severe TOD.
- In patients with T2DM without symptomatic ASCVD or severe TOD, 10-year CVD risk via SCORE2-Diabetes should be calculated.

Lifestyle

- For smokers, smoking cessation is a primary target of lifestyle intervention in patients with CVD and diabetes.
- Exercise should be introduced in all patients with CVD and T2DM, following the paradigm 'every step counts'.
- In patients with obesity and T2DM with or without CVD, reducing weight combined with increasing daily PA through structured exercise sessions are key lifestyle components to improve metabolic control, improve exercise capacity, and reduce clinical outcomes.
- A Mediterranean diet supplemented with olive oil and/or nuts reduces the incidence of major CV events in patients with CVD.

Glycaemic targets

- Tight glycaemic control reduces short- and long-term microvascular disease.
- Tight glycaemic control reduces long-term macrovascular complications (over 20 years).
- Hypoglycaemia is associated with adverse CV outcomes and is best avoided.

Glucose-lowering therapy

- ASCVD complications are common in patients with T2DM.
- Glycaemic status should be systematically evaluated in all patients with or at high risk of CVD, as diabetes status informs many clinical decisions in cardiology.
- Independent of baseline HbA1c or additional glucose-lowering agents, selected SGLT2 inhibitors and GLP-1 RAs reduce CV events in patients with T2DM with ASCVD and/or severe TOD.

Blood pressure

- BP targets should be individualized for hypertensive patients.
- Optimal BP control reduces the risk of micro- and macrovascular complications.
- Controlling BP often requires multiple drug therapies with an RAS inhibitor, and a CCB or diuretic. Dual therapy is recommended as first-line treatment.
- All hypertensive patients with diabetes, irrespective of their antihypertensive treatments, should monitor their BP at home.

Lipids

- Statins remain the first-line and state-of-the-art therapy to decrease LDL-C levels.
- Ezetimibe and PCSK9 inhibitors in addition to statins (if treatment targets have not been achieved)—or alone (in case of documented

intolerance to statins)—significantly reduce LDL-C levels, thus improving CV outcomes.

Antithrombotic therapy

- Based on the presence of ASCVD and individual CV risk, antiplatelet agents are a cornerstone of preventing CV events in patients with diabetes.
- Shortening or scaling down DAPT to clopidogrel should be avoided in patients with diabetes post-ACS, given their high background CV risk, the lack of efficacy data, and the poor bio-activation of clopidogrel.
- Platelet-function testing guided de-escalation should be avoided based on lack of evidence and poor bio-activation of clopidogrel.

Multifactorial approach

- Continuous, multidisciplinary counselling is necessary to achieve long-term lifestyle changes.

Management of coronary artery disease

- In patients with CAD, SGLT2 inhibitors and/or GLP-1 RAs reduce the risk of CV events.
- In patients with diabetes and multivessel CAD, suitable coronary anatomy for revascularization, and low predicted surgical mortality, CABG is superior to PCI.

Heart failure

- The prognosis of patients with diabetes and HF is worse compared with patients with HF without diabetes.
- Beta-blockers, ARNI/ACE-Is, MRAs, and SGLT2 inhibitors are recommended as cornerstone therapies for patients with HFrEF and diabetes.
- Empagliflozin and dapagliflozin reduce the combined endpoint of CV death or HF hospitalization in patients with HF and a LVEF >40%.
- Glucose-lowering treatment with SGLT2 inhibitors in patients with diabetes and HF reduces HF-related endpoints.
- Saxagliptin and pioglitazone increase the risk of HF hospitalization in patients with diabetes and HF.

Arrhythmias

- AF is common in patients with diabetes, and increases mortality, risk of stroke, and risk of HF.
- Opportunistic screening for AF is recommended for patients with diabetes aged ≥65 years by palpating pulse (or using wearable devices) and systematic ECG screening when age is ≥75 years. AF should always be confirmed by ECG.
- Opportunistic screening for AF by pulse taking or ECG is recommended in patients with diabetes aged <65 years in view of their risk of AF and the possibly associated risk of ischaemic stroke.

Chronic kidney disease

- CKD in patients with diabetes is associated with high risk of developing kidney failure and CVD.
- Patients with diabetes should be regularly screened for CKD, or have their CKD staged, by assessing eGFR and UACR.
- Certain ACE-I/ARBs, SGLT2 inhibitors, and finerenone reduce the risk of kidney failure and the risk of CVD in patients with T2DM and CKD.

Aortic and peripheral arterial diseases

- LEAD is a common complication in patients with diabetes and associated with poorer prognosis.
- Patients with diabetes are at higher risk of CLTI as the first clinical manifestation of LEAD, supporting regular screening with ABI measurement for early diagnosis.
- The management of patients with LEAD and indications for different treatment strategies are similar in patients with or without diabetes, although the options for revascularization may be poorer in patients with diabetes because of diffuse and distal lesions.

Type 1 diabetes

- Glucose-lowering therapy in T1DM should follow principles of patient self-management under the guidance of the diabetes healthcare multidisciplinary team.

Person-centred care

- A person-centred approach is a key factor in successful self-management, resulting in greater patient satisfaction, adherence to therapeutic plans, and improved health outcomes.
- Important factors for self-management of diabetes and comorbidities are education, motivation, empowerment, and continuing supportive care of individuals.

15. Gaps in evidence

Diagnosis of diabetes

- Global screening programmes for diabetes, adjusted for regional demographics and ethnic groups, are required to establish the most accurate and cost-effective screening test.

Lifestyle

- RCTs of long-term exercise intervention to reduce CV outcomes are needed in different patient groups with diabetes and CVD, e.g. CAD, HFpEF, HFrEF, AF, or PAD.
- Large RCTs assessing the benefit of a multidisciplinary team to increase adherence to lifestyle interventions and optimal medication are needed in patients with T2DM and CVD.
- The applicability and best practice of telehealth needs to be evaluated in elderly and frail patients with T2DM and CVD.

Glycaemic targets

- The independent role of hypoglycaemia, glycaemic variability, time-in-range, and post-prandial hyperglycaemia in CV pathology requires further research.
- Large-scale studies are required to understand the role of modern glucose-monitoring strategies (CGM) in improving macrovascular and HF outcomes.

Glucose-lowering therapy

- It remains unclear if the combination therapy of GLP-1 RAs and SGLT2 inhibitors is complementary in cardio-renal outcomes in patients with T2DM.
- It needs to be examined if more intensive glycaemic control, achieved with novel medications, might prove to have incremental CV efficacy.

Blood pressure

- High-quality data on managing BP in T1DM are lacking.
- Optimal targets for (isolated) DBP in patients with diabetes and hypertension remain inconclusive.
- More information on optimizing CV protection in diabetes by managing BP based on out-of-office BP levels should be provided by randomized intervention trials.

Lipids

- Optimal LDL-C target levels for patients with diabetes need to be established; good scientific evidence is especially missing in T1DM.
- Novel lipid-lowering drugs, such as inclisiran need efficacy data on CV endpoints both in the general population and in patients with diabetes.

Antithrombotic therapy

- More data on primary CV prevention are needed for patients with T1DM.
- Future phase 3 RCTs testing antithrombotic drugs in CV prevention should share homogeneous classifications of bleeding to make the benefit-risk profile of mono- or combined therapy comparable across different studies.
- The benefit-risk profile of ASA in CV prevention in patients with diabetes, documented significant atherosclerotic lesions (peripheral or coronary), or high CAC score but without history of stroke or MI should be further investigated in RCTs.
- Since documented kidney and/or eye microvascular disease independently predict future CV events, it needs to be assessed whether patients with diabetes with microvascular disease and no history of MACE would benefit from early primary prophylaxis.
- It needs to be demonstrated in adequately powered, superiority, efficacy-based RCTs whether 12-month DAPT post-ACS can be reduced to a shorter period in patients with diabetes using SAPT with ASA or with a $P2Y_{12}$ inhibitor.
- The optimal duration of TAT post-ACS in patients with diabetes and AF needs to be established.

Multifactorial approach

- An optimal intervention protocol to improve adherence remains to be established, particularly addressing patients with diabetes and comorbidities, and the elderly population.
- Sex and ethnicity differences regarding efficacy of multifactorial interventions need to be evaluated.
- Evaluation of E-health applications to improve adherence to lifestyle intervention and medication also assessing clinical outcomes is needed in patients with CVD and diabetes.

Management of coronary artery disease

- Optimal glycaemic control and in-hospital anti-glycaemic strategies for the outcomes of ACS and stable CAD, as well as after coronary revascularization, remain to be established.
- Although newer-generation DES have improved outcomes in patients with diabetes, RCTs are needed to determine whether they can reduce the gap in outcomes between CABG and PCI.
- No direct comparison RCT has focused on revascularization in patients with diabetes and left main disease.
- Robust data on patients with CAD and T1DM are missing.
- The effect of anti-inflammatory strategies in patients with diabetes should be assessed in dedicated trials.

Heart failure

- The effect of finerenone on cardio-renal endpoints in patients with diabetes and HFrEF or HFpEF needs to be examined.
- More mechanistic studies are warranted to better understand how SGLT2 inhibitors improve HF outcomes.
- Research is needed to guide OMT in patients with HF and T1DM.
- The prognostic benefit of HF screening with BNP/NT-proBNP in asymptomatic patients with diabetes needs to be determined.

Arrhythmias

- Better evidence is needed regarding the risks of atrial and ventricular arrhythmias associated with T1DM and how they should be optimally managed.
- Optimal screening methods and treatment for patients with diabetes still need to be defined in RCTs.
- The role of AF in diabetes needs to be evaluated in CVOTs.
- Whether SGLT2 inhibitors reduce the risk of CV death by reducing the risk of ventricular tachyarrhythmias should be more precisely evaluated.

Chronic kidney disease

- CV and renal effects of using non-steroidal MRAs in patients with CKD on a combined ACE-I/ARB + SGLT2-inhibitor regimen need to be explored.
- Net benefits of antiplatelet therapy in patients with diabetes and CKD with and without ASCVD need to be examined.

Aortic and peripheral arterial diseases

- The frequency and mode of vascular screening in patients with diabetes needs to be assessed.
- Specific trials are needed to help clinicians choose different pharmacological strategies according to the presence of PAD.

Type 1 diabetes

- Comprehensive cardio-protection management in patients with early-onset T1DM needs to be evaluated.
- The role of ameliorating insulin resistance and using adjunctive therapies to reduce CV risk remains to be elucidated.
- Lifestyle intervention trials in patients with T1DM and CVD are lacking.

Person-centred care

- Better CVD management of women with diabetes is needed.
- Effective interdisciplinary approaches to better manage glycaemic control and minimize the risk of complications are required.
- Data are lacking on personalization of mobile Health (mHealth) by assessing how individual factors, such as health literacy, culture, socioeconomic status, ageing, behaviours, and treatment plan, impact patient engagement with mHealth tools and clinical outcomes.

16. Sex differences

Epidemiological studies suggest that diabetes is a stronger risk factor for CVD in women compared with men. Data from large CVOTs do not suggest sex differences with respect to the benefit of CV risk-reducing

strategies in T2DM, i.e. treatment with SGLT2 inhibitors or GLP-1 RAs. Although women are under-represented in clinical trials, there is no evidence for sex-specific recommendations for managing CVD in patients with diabetes. However, epidemiological and real-world data suggest that guideline-directed therapy in women is less likely to be applied compared with men.[835–837] This should be explored in future studies. Therefore, we recommend implementing sex-balanced recruitment strategies for future CVOTs. In addition, pre-specified analyses addressing sex differences are needed. Most importantly, every effort should be made to ensure women receive equal healthcare opportunities in managing CVD in diabetes.

17. 'What to do' and 'What not to do' messages from the Guidelines

Table 12 'What to do' and 'What not to do'

Recommendations	Class[a]	Level[b]
Recommendations for diagnosis of diabetes		
Screening for diabetes is recommended in all individuals with CVD, using fasting glucose and/or HbA1c.	I	A
It is recommended that the diagnosis of diabetes is based on HbA1c and/or fasting plasma glucose, or on an OGTT if still in doubt.	I	B
Recommendations for assessing cardiovascular risk in patients with diabetes		
It is recommended to screen patients with diabetes for the presence of severe TOD.	I	A
It is recommended to assess medical history and the presence of symptoms suggestive of ASCVD in patients with diabetes.	I	B
In patients with T2DM without symptomatic ASCVD or severe TOD, it is recommended to estimate 10-year CVD risk via SCORE2-Diabetes.	I	B
Recommendations for weight reduction in patients with diabetes		
It is recommended that individuals living with overweight or obesity aim to reduce weight and increase physical exercise to improve metabolic control and overall CVD risk profile.	I	A
Recommendations for nutrition in patients with diabetes		
It is recommended to adopt a Mediterranean or plant-based diet with high unsaturated fat content to lower cardiovascular risk.	I	A
Recommendation for physical activity/exercise in patients with diabetes		
It is recommended to increase any physical activity (e.g. 10 min daily walking) in all patients with T2DM with and without CVD. Optimal is a weekly activity of 150 min of moderate intensity or 75 min of vigorous endurance intensity.	I	A
It is recommended to adapt exercise interventions to T2DM-associated comorbidities, e.g. frailty, neuropathy, or retinopathy.	I	B
It is recommended to introduce structured exercise training in patients with T2DM and established CVD, e.g. CAD, HFpEF, HFmrEF, HFrEF, or AF to improve metabolic control, exercise capacity and quality of life, and to reduce CV events.	I	B
It is recommended to perform resistance exercise in addition to endurance exercise at least twice a week.	I	B
Recommendation for smoking cessation in patients with diabetes		
It is recommended to stop smoking to reduce cardiovascular risk.	I	A
Recommendations for glycaemic targets		
It is recommended to apply tight glycaemic control (HbA1c <7%) to reduce microvascular complications.	I	A
It is recommended to avoid hypoglycaemia, particularly in patients with CVD.	I	B
It is recommended to individualize HbA1c targets according to comorbidities, diabetes duration, and life expectancy.	I	C
Recommendations for glucose-lowering treatment for patients with type 2 diabetes and atherosclerotic cardiovascular disease to reduce cardiovascular risk		
It is recommended to prioritize the use of glucose-lowering agents with proven CV benefits followed by agents with proven CV safety over agents without proven CV benefit or proven CV safety.	I	C
Sodium–glucose co-transporter-2 inhibitors		
SGLT2 inhibitors with proven CV benefit are recommended in patients with T2DM and ASCVD to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.	I	A
Glucagon-like peptide-1 receptor agonists		
GLP-1 RAs with proven CV benefit are recommended in patients with T2DM and ASCVD to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.	I	A

Continued

Recommendations for blood pressure in patients with diabetes		
Screening for hypertension		
Regular BP measurements are recommended in all patients with diabetes to detect and treat hypertension to reduce CV risk.	I	A
Treatment targets		
Anti-hypertensive drug treatment is recommended for people with diabetes when office BP is ≥140/90 mmHg.	I	A
It is recommended to treat hypertension in patients with diabetes in an individualized manner. The BP goal is to target SBP to 130 mmHg and <130 mmHg if tolerated, but not <120 mmHg. In older people (age >65 years), it is recommended to target SBP to 130–139 mmHg.	I	A
Treatment and evaluation		
Lifestyle changes (weight loss if overweight, physical activity, alcohol restriction, sodium restriction, increased consumption of vegetables, using low-fat dairy products) are recommended in patients with diabetes and hypertension.	I	A
It is recommended to initiate treatment with a combination of an RAS inhibitor and a CCB or thiazide/thiazide-like diuretic.	I	A
Recommendations for lipids and diabetes		
Lipid targets in patients with diabetes		
In patients with T2DM at moderate CV risk, an LDL-C target of <2.6 mmol/L (<100 mg/dL) is recommended.	I	A
In patients with T2DM at high CV risk, an LDL-C target of <1.8 mmol/L (<70 mg/dL) and LDL-C reduction of at least 50% is recommended.	I	A
In patients with T2DM at very high CV risk, an LDL-C target of <1.4 mmol/L (<55 mg/dL) and LDL-C reduction of at least 50% is recommended.	I	B
In patients with T2DM, a secondary goal of a non-HDL-C target of <2.2 mmol/L (<85 mg/dL) in very high CV risk patients, and <2.6 mmol/L (<100 mg/dL) in high CV risk patients, is recommended.	I	B
Lipid-lowering treatment in patients with diabetes		
Statins are recommended as the first-choice LDL-C-lowering treatment in patients with diabetes and above-target LDL-C levels. Administration of statins is defined based on the CV risk profile of the patients and the recommended LDL-C (or non-HDL-C) target levels.	I	A
A PCSK9 inhibitor is recommended in patients at very high CV risk, with persistently high LDL-C levels above target despite treatment with a maximum tolerated statin dose, in combination with ezetimibe, or in patients with statin intolerance.	I	A
If the target LDL-C is not reached with statins, combination therapy with ezetimibe is recommended.	I	B
Recommendations for antithrombotic therapy in patients with diabetes and acute or chronic coronary syndrome without indications for long-term oral anticoagulation		
ASA at a dose of 75–100 mg o.d. is recommended in patients with diabetes and previous MI or revascularization (CABG or stenting).	I	A
In patients with ACS and diabetes who undergo PCI, a $P2Y_{12}$ receptor inhibitor (ticagrelor or prasugrel) is recommended in addition to ASA (75–100 mg o.d.), maintained over 12 months.	I	A
Clopidogrel 75 mg o.d. following appropriate loading (e.g. 600 mg or at least 5 days already on maintenance therapy) is recommended in addition to ASA for 6 months following coronary stenting in patients with CCS, irrespective of stent type, unless a shorter duration is indicated due to the risk or occurrence of life-threatening bleeding.	I	A
Clopidogrel is recommended as an alternative in case of ASA intolerance.	I	B
In patients with diabetes and ACS treated with DAPT who are undergoing CABG and do not require long-term OAC therapy, resuming a $P2Y_{12}$ receptor inhibitor as soon as deemed safe after surgery and continuing it up to 12 months is recommended.	I	C
Recommendations for antithrombotic therapy in patients with diabetes and acute or chronic coronary syndrome and/or post-percutaneous coronary intervention requiring long-term oral anticoagulation		
In patients with AF and receiving antiplatelet therapy, eligible for anticoagulation, and without a contraindication, NOACs are recommended in preference to a VKA.	I	A
In patients with ACS or CCS and diabetes undergoing coronary stent implantation and having an indication for anticoagulation, triple therapy with low-dose ASA, clopidogrel, and an OAC is recommended for at least 1 week, followed by dual therapy with an OAC and a single, oral, antiplatelet agent.	I	A
Recommendations for gastric protection		
When antithrombotic drugs are used in combination, proton pump inhibitors are recommended to prevent gastrointestinal bleeding.	I	A
When clopidogrel is used, omeprazole and esomeprazole are not recommended for gastric protection.	III	B
Recommendations for a multifactorial approach in patients with diabetes		
Identifying and treating risk factors and comorbidities early is recommended.	I	A
A multifactorial approach to managing T2DM with treatment targets is recommended.	I	B
Multidisciplinary behavioural approaches that combine the knowledge and skills of different caregivers are recommended.	I	C

Continued

Recommendations for revascularization in patients with diabetes		
It is recommended that similar revascularization techniques are implemented (e.g. the use of DES and the radial approach for PCI, and the use of the left internal mammary artery as the graft for CABG) in patients with and without diabetes.	I	A
Myocardial revascularization in CCS is recommended when angina persists despite treatment with anti-anginal drugs or in patients with a documented large area of ischaemia (>10% LV).	I	A
Complete revascularization is recommended in patients with STEMI without cardiogenic shock and with multivessel CAD.	I	A
Routine immediate revascularization of non-culprit lesions in patients with MI with multivessel disease presenting with cardiogenic shock is not recommended.	III	B
Recommendations for glycaemic control in patients with diabetes and acute coronary syndrome		
It is recommended to assess glycaemic status at initial evaluation in all patients with ACS.	I	B
It is recommended to frequently monitor blood glucose levels in patients with known diabetes or hyperglycaemia (defined as glucose levels ≥11.1 mmol/L or ≥200 mg/dL).	I	C
Recommendations for heart failure screening and diagnosis in patients with diabetes		
Evaluation for heart failure		
If HF is suspected, it is recommended to measure BNP/NT-proBNP.	I	B
Systematic survey for HF symptoms and/or signs of HF is recommended at each clinical encounter in all patients with diabetes.	I	C
Diagnostic tests in all patients with suspected heart failure		
12-lead ECG is recommended.	I	C
Transthoracic echocardiography is recommended.	I	C
Chest radiography (X-ray) is recommended.	I	C
Routine blood tests for comorbidities are recommended, including full blood count, urea, creatinine and electrolytes, thyroid function, lipids, and iron status (ferritin and TSAT).	I	C
Recommendations for heart failure treatments in patients with heart failure with reduced ejection fraction and diabetes		
Recommendations for pharmacological treatment indicated in patients with HFrEF (NYHA class II–IV) and diabetes		
SGLT2 inhibitors (dapagliflozin, empagliflozin, or sotagliflozin) are recommended in all patients with HFrEF and T2DM to reduce the risk of HF hospitalization and death.	I	A
Sacubitril/valsartan or an ACE-I is recommended in all patients with HFrEF and diabetes to reduce the risk of HF hospitalization and death.	I	A
Beta-blockers are recommended in patients with HFrEF and diabetes to reduce the risk of HF hospitalization and death.	I	A
MRAs are recommended in patients with HFrEF and diabetes to reduce the risk of HF hospitalization and death.	I	A
An intensive strategy of early initiation of evidence-based treatment (SGLT2 inhibitors, ARNI/ACE-Is, beta-blockers, and MRAs), with rapid up-titration to trial-defined target doses starting before discharge and with frequent follow-up visits in the first 6 weeks following a HF hospitalization is recommended to reduce re-admissions or mortality.	I	B
Recommendations for other treatments indicated in selected patients with HFrEF (NYHA class II–IV) and diabetes		
Device therapy with an ICD, CRT-P, or CRT-D is recommended in patients with diabetes, as in the general population with HFrEF.	I	A
ARBs are recommended in symptomatic patients with HFrEF and diabetes who do not tolerate sacubitril/valsartan or ACE-Is, to reduce the risk of HF hospitalization and death.	I	A
Diuretics are recommended in patients with HFrEF and diabetes with signs and/or symptoms of fluid congestion to improve symptoms, exercise capacity, and HF hospitalization.	I	C
Recommendations for the treatment of heart failure patients with left ventricular ejection fraction >40% and diabetes		
Empagliflozin or dapagliflozin are recommended in patients with T2DM and LVEF >40% (HFmrEF and HFpEF) to reduce the risk of HF hospitalization or CV death.	I	A
Diuretics are recommended in patients with HFpEF or HFmrEF and diabetes with signs and/or symptoms of fluid congestion to improve symptoms, exercise capacity, and HF hospitalization.	I	C
Recommendations for glucose-lowering medications in patients with type 2 diabetes with and without heart failure		
Recommendations for glucose-lowering medications to reduce heart failure hospitalization in patients with type 2 diabetes with or without existing heart failure		
SGLT2 inhibitors (empagliflozin, canagliflozin, dapagliflozin, ertugliflozin, or sotagliflozin) are recommended in patients with T2DM with multiple ASCVD risk factors or established ASCVD to reduce the risk of HF hospitalization.	I	A
SGLT2 inhibitors (dapagliflozin, empagliflozin, or sotagliflozin) are recommended in patients with T2DM and HFrEF to reduce the risk of HF hospitalization and death.	I	A

Continued

Empagliflozin or dapagliflozin are recommended in patients with T2DM and LVEF >40% (HFmrEF and HFpEF) to reduce the risk of HF hospitalization or CV death.	I	A
Recommendations for glucose-lowering medications with an increased risk of heart failure hospitalization in patients with type 2 diabetes		
Pioglitazone is associated with an increased risk of incident HF in patients with diabetes and is not recommended for glucose-lowering treatment in patients at risk of HF (or with previous HF).	III	A
The DPP-4 inhibitor saxagliptin is associated with an increased risk of HF hospitalization in patients with diabetes and is not recommended for glucose-lowering treatment in patients at risk of HF (or with previous HF).	III	B
Recommendations for special consideration in patients with heart failure and diabetes		
It is recommended to switch glucose-lowering treatment from agents without proven CV benefit or proven safety to agents with proven CV benefit.	I	C
Recommendations for atrial fibrillation in patients with diabetes		
Screening for atrial fibrillation in diabetes		
Opportunistic screening for AF by pulse taking or ECG is recommended in patients ≥65 years of age.	I	B
Opportunistic screening for AF by pulse taking or ECG is recommended in patients with diabetes <65 years of age (particularly when other risk factors are present) because patients with diabetes exhibit a higher AF frequency at a younger age.	I	C
Anticoagulation for atrial fibrillation in patients with diabetes		
Oral anticoagulation is recommended for preventing stroke in patients with AF and diabetes and with at least one additional (CHA_2DS_2-VASc) risk factor for stroke.	I	A
For preventing stroke in AF, NOACs are recommended in preference to VKAs, with the exception of patients with mechanical valve prostheses or moderate to severe mitral stenosis.	I	A
Recommendations for patients with chronic kidney disease and diabetes		
Intensive LDL-C lowering with statins or a statin/ezetimibe combination is recommended.	I	A
A BP target of ≤130/80 mmHg is recommended to reduce risk of CVD and albuminuria.	I	A
Personalized HbA1c targets 6.5–8.0% (48–64 mmol/mol) are recommended, with a target <7.0% (<53 mmol/mol) to reduce microvascular complications, wherever possible.	I	A
The maximum tolerated dose of an ACE-I or ARB is recommended.	I	A
A SGLT2 inhibitor (canagliflozin, empagliflozin, or dapagliflozin) is recommended in patients with T2DM and CKD with an eGFR ≥20 mL/min/1.73 m^2 to reduce the risk of CVD and kidney failure.	I	A
Finerenone is recommended in addition to an ACE-I or ARB in patients with T2DM and eGFR >60 mL/min/1.73 m^2 with a UACR ≥30 mg/mmol (≥300 mg/g), or eGFR 25–60 mL/min/1.73 m^2 and UACR ≥3 mg/mmol (≥30 mg/g) to reduce CV events and kidney failure.	I	A
A GLP-1 RA is recommended at eGFR >15 mL/min/1.73 m^2 to achieve adequate glycaemic control, due to low risk of hypoglycaemia and beneficial effects on weight, CV risk, and albuminuria.	I	A
Low-dose ASA (75–100 mg o.d.) is recommended in patients with CKD and ASCVD.	I	A
It is recommended that patients with diabetes are routinely screened for kidney disease by assessing eGFR defined by CKD-EPI and UACR.	I	B
Treatment with intensive medical or an initial invasive strategy is recommended in people with CKD, diabetes, and stable moderate or severe CAD, due to similar outcomes.	I	B
Combined use of an ARB with an ACE-I is not recommended.	III	B
Recommendations for aortic and peripheral arterial diseases and diabetes		
Lower-extremity artery disease in patients with diabetes		
In patients with diabetes and symptomatic LEAD, antiplatelet therapy is recommended.	I	A
In patients with diabetes and CLTI, it is recommended to assess the risk of amputation; the WIfI score is useful for this purpose.	I	B
As patients with diabetes and LEAD are at very high CV risk, an LDL-C target of <1.4 mmol/L (<55 mg/dL) and an LDL-C reduction of at least 50% is recommended.	I	B
Screening for LEAD is recommended on a regular basis, with clinical assessment and/or ABI measurement.	I	C
Patient education about foot care is recommended in patients with diabetes, and especially those with LEAD, even if asymptomatic. Early recognition of tissue loss and/or infection, and referral to a multidisciplinary team, is mandatory to improve limb salvage.	I	C
An ABI ≤0.90 is diagnostic of LEAD, irrespective of symptoms. In symptomatic cases, further assessment including duplex ultrasound is recommended.	I	C
When ABI is elevated (>1.40), other non-invasive tests, including TBI or duplex ultrasound, are recommended.	I	C
Duplex ultrasound is recommended as the first-line imaging method to assess the anatomy and haemodynamic status of lower-extremity arteries.	I	C

Continued

In case of CLTI, revascularization is recommended whenever feasible for limb salvage.	I	C
Carotid artery disease in patients with diabetes		
In patients with diabetes and carotid artery disease, it is recommended to implement the same diagnostic work-up and therapeutic strategies (medical, surgical, or endovascular) as in patients without diabetes.	I	C
Aortic aneurysm in patients with diabetes		
In patients with diabetes and aortic aneurysm, it is recommended to implement the same diagnostic work-up and therapeutic strategies (medical, surgical, or endovascular) as in patients without diabetes.	I	C
Recommendations for type 1 diabetes and cardiovascular disease		
In patients with T1DM, it is recommended that adjustment of glucose-lowering medication follows principles of patient self-management under the guidance of the diabetes healthcare multidisciplinary team.	I	C
Avoiding hypoglycaemic episodes is recommended, particularly in those with established CVD.	I	C
Recommendations for person-centred care in diabetes		
Structured education programmes are recommended in patients with diabetes to improve diabetes knowledge, glycaemic control, disease management, and patient empowerment.	I	A
Person-centred care is recommended to facilitate shared control and decision-making within the context of person priorities and goals.	I	C

ABI, ankle–brachial index; ACE-I, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AF, atrial fibrillation; ARB, angiotensin-II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; ASA, acetylsalicylic acid; ASCVD, atherosclerotic cardiovascular disease; BNP, B-type natriuretic peptide; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCB, calcium channel blocker; CCS, chronic coronary syndrome; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes mellitus, Stroke or transient ischaemic attack (2 points), Vascular disease, Age 65–74 years, Sex category (female); CKD, chronic kidney disease; CKD-EPI, chronic kidney disease epidemiology; CLTI, chronic limb-threatening ischaemia; CRT-D, cardiac resynchronization therapy with an implantable defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; CV, cardiovascular; CVD, cardiovascular disease; DAPT, dual antiplatelet therapy; DES, drug-eluting stents; DPP-4, dipeptidyl peptidase-4; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein-cholesterol; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; LEAD, lower-extremity artery disease; LDL-C, low-density lipoprotein-cholesterol; LV, left ventricle; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NOAC, non-vitamin K antagonist oral anticoagulant; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OAC, oral anticoagulant; o.d., once daily; OGTT, oral glucose tolerance test; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin/kexin type 9; RAS, renin–angiotensin system; SBP, systolic blood pressure; SCORE2-Diabetes, type 2 diabetes-specific 10-year CVD risk score; SGLT2, sodium–glucose co-transporter-2; STEMI, ST-elevation myocardial infarction; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TBI, toe–brachial index; TOD, target-organ damage; TSAT, transferrin saturation; UACR, urinary albumin-to-creatinine ratio; VKA, vitamin K antagonist; WIfI, Wound, Ischaemia, foot Infection.

[a]Class of recommendation.

[b]Level of evidence.

18. Quality indicators

Quality indicators (QIs) are tools that may be used to evaluate care quality, including structural, process, and outcomes of care.[838] They may also serve as a mechanism for enhancing adherence to Guideline recommendations, through associated quality-improvement initiatives and benchmarking of care clinicians.[839,840] As such, the role of QIs in improving care and outcomes for CVD is increasingly recognized by healthcare authorities, professional organizations, payers, and the public.[838]

The ESC understands the need for measuring and reporting quality and outcomes of CV care and has established methods for developing the ESC QIs for quantifying care and outcomes for CVDs.[838] To date, the ESC has developed QI suites for a number of CVDs in parallel with writing the ESC Clinical Practice Guidelines.[841–844]

The ESC aims to harmonize its QIs for various CV conditions and integrate them with ESC registries, providing real-world data about the patterns and outcomes of care for CVD across Europe.[845]

19. Supplementary data

Supplementary data is available at *European Heart Journal* online.

20. Data availability statement

No new data were generated or analysed in support of this research.

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22. Appendix

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24. References

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