Cardiovascular Risk Reduction in Patients with Type 2 Diabetes: What Does the Cardiologist Need to Know?

Martin Berger, Nikolaus Marx and Katharina Marx-Schütt

Department of Internal Medicine I, University Hospital Aachen, Aachen, Germany

Abstract

Patients with diabetes are at an increased risk of cardiovascular disease (CVD), including atherosclerotic CVD and heart failure. In addition, diabetes is associated with a higher risk of developing chronic kidney disease, which is considered to be one of the strongest risk factors for CVD and mortality. To address the increased cardiovascular risk of patients with diabetes, dedicated screening strategies for CVD are necessary; conversely, screening for diabetes needs to be performed in all patients with CVD to allow timely identification. Once diabetes is diagnosed, rapid implementation of treatment with therapies to reduce cardiovascular risk on top of standard of care is necessary. This review gives an overview of contemporary therapeutic strategies to reduce cardiovascular risk in patients with type 2 diabetes.

Keywords

Diabetes, cardiovascular risk reduction, chronic kidney disease, heart failure

Received: 20 June 2024 **Accepted:** 29 November 2024 **Citation:** *European Cardiology Review* 2025;20:e09. **DOI:** https://doi.org/10.15420/ecr.2024.29

Disclosures: NM has given lectures for Bayer, Boehringer Ingelheim, Sanofi-Aventis, MSD, BMS, AstraZeneca, Lilly and Novo Nordisk; has received unrestricted research grants from Boehringer Ingelheim; has served as an adviser for Bayer, Boehringer Ingelheim, Sanofi-Aventis, MSD, BMS, AstraZeneca and Novo Nordisk; has served in a trial leadership position for Boehringer Ingelheim and Novo Nordisk; and declines all personal compensation from pharmaceutical or device companies. KMS has received personal fees for lectures from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Lilly, MSD, Novo Nordisk, Novartis and OmniaMed; and has served as an adviser for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim and Novo Nordisk. MB has no conflicts of interest to disclose.

Funding: NM is supported by the Deutsche Forschungsgemeinschaft (German Research Foundation), TRR 219, project ID 322900939 [M03, M05]. KMS is supported by the Deutsche Forschungsgemeinschaft (German Research Foundation), TRR 219, project ID 322900939 [C07].

Correspondence: Nikolaus Marx, Department of Internal Medicine I, University Hospital Aachen, RWTH Aachen University, Pauwelsstrasse 30, 52074 Aachen, Germany. E: nmarx@ukaachen.de

Patients with diabetes are at increased risk of cardiovascular disease (CVD) and the presence of diabetes is associated with a two- to three-fold increase in cardiovascular (CV) events.[1]

Type 2 diabetes (T2D) is the most frequent presentation of diabetes and accounts for 90% of all cases. It is characterised by hyperglycaemia resulting from tissue insulin resistance and relative insulin deficiency.[2] In 2021, 537 million individuals were affected by T2D and this is predicted to rise to 783 million cases by 2045.[3]

The predominant CVD manifestations in T2D are atherosclerotic cardiovascular disease (ASCVD) and heart failure (HF). In addition, the presence of T2D is linked to chronic kidney disease (CKD), which itself is considered one of the strongest risk factors for CV disease and mortality (*Figure 1*).[4]

Therefore, it is of utmost importance to systematically screen patients with diabetes for CVD and HF, as well as to assess them for CKD.[5] Over the past decade, large-scale CV outcome trials (CVOTs) have demonstrated a significant CV risk reduction in patients with T2D with the new glucose-lowering drugs sodium-glucose co-transporter-2 inhibitors (SGLT2Is) and glucagon-like peptide-1 (GLP-1) receptor agonists (RAs), as well as the novel non-steroidal mineralocorticoid receptor antagonist finerenone.[6,7]

This article provides an updated overview of CVD, HF and CKD in the context of T2D and discusses current therapeutic strategies to reduce CV risk in these patients, with a special focus on SGLT2Is, GLP-1 RAs and finerenone.

Screening for Comorbidities in Type 2 Diabetes

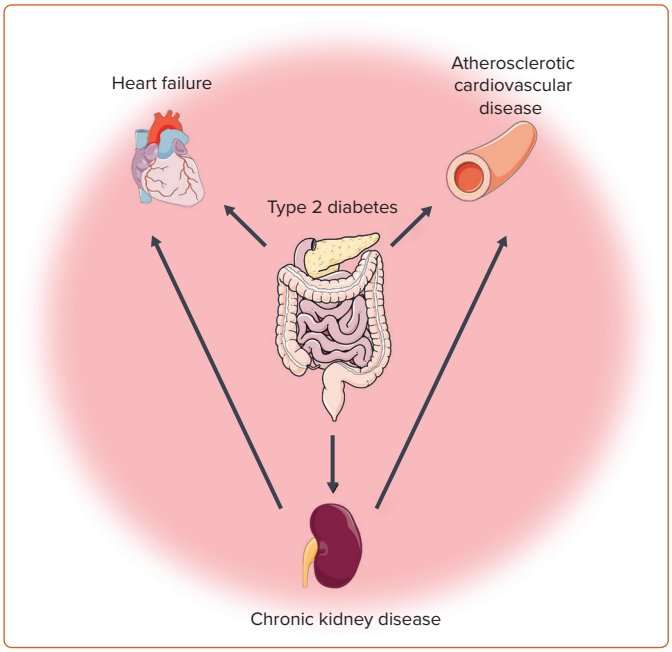
CVD and CKD are the predominant causes of mortality and morbidity in patients with T2D. Given the novel pharmacological approaches for patients with T2D, a comprehensive awareness of comorbidities, including ASCVD, heart failure (HF) and CKD, is obligatory to tailor therapy so it is prognostically relevant (*Figure 2*).[5]

Atherosclerotic Cardiovascular Disease

Data on screening for ASCVD in people with diabetes are conflicting, and non-invasive routine screening is not recommended for asymptomatic patients until evidence from larger trials becomes available.[8]

Nonetheless, diabetes is an important risk factor for ASCVD. CT data from 510 asymptomatic diabetes patients suggested that 46% had coronary atherosclerosis.[9] Therefore, a systematic survey of angina episodes is a reasonable approach to guide further invasive and non-invasive testing for ASCVD in all patients with diabetes.[10]

Figure 1: Interplay between Diabetes, Atherosclerotic Cardiovascular Disease, Heart Failure and Chronic Kidney Disease



Created using images from Servier Medical Art. Reproduced under a Creative Commons CC BY 4.0 licence.

Conversely, given the increased prevalence of diabetes in patients with ASCVD, in particular in those with acute coronary syndrome, all patients should be tested for diabetes.[5,11]

Heart Failure

In patients with T2D, a systematic survey for HF symptoms (e.g. breathlessness, exertional dyspnoea or fatigue) and clinical signs of HF (e.g. weight gain, peripheral oedema, elevated jugular venous pulse, third heart sound or hepatojugular reflux) is recommended. When signs are present, brain natriuretic peptide (BNP) or NT-proBNP levels should be measured; these will guide further testing by echocardiography when elevated (i.e. BNP ≥35 pg/ml; NT–proBNP ≥125 pg/ml).[5]

In addition, 10–47% of patients with HF are diagnosed with diabetes.[12] Therefore, all HF patients should be tested for diabetes.

Chronic Kidney Disease

Screening for CKD should be conducted at least annually in patients with T2D.[5]

Measurement of serum creatinine is necessary to calculate the estimated glomerular filtration rate (eGFR), which provides an overview of kidney function. Additionally, albumin excretion should be evaluated., with the urine albumin:creatinine ratio (UACR) being a reliable and accessible method that allows risk stratification and predicts both kidney failure and CVD independent of eGFR.[13]

Atherosclerotic Cardiovascular Disease in Patients with Type 2 Diabetes

Patients with diabetes have an increased risk of ASCVD, and coronary artery disease accounts for 40–80% of deaths in those with T2D.[14] Haffner et al. demonstrated in 1998 that patients with T2D had a similar risk of future MI and fatal CVD as patients without T2D but with previous MI.[15] While this observation was influenced by a distinct T2D population with extensive comorbidities and long-standing histories of T2D, it underlined the vulnerability of T2D patients with regards to ASCVD and, in particular, coronary artery disease.

Given the close relationship between diabetes and ASCVD, current guidelines recommend systematically screening for the presence of diabetes in all patients with ASCVD.[5]

Atherosclerotic Cardiovascular Risk Reduction with Glucose-lowering Medications

The link between ASCVD and diabetes is well established and research suggests that, among other mechanisms, hyperglycaemia-induced endothelial dysfunction, oxidative stress and inflammation have a role.[16]

However, the relationship between CV risk reduction and pharmacological glucose control in patients with T2D remains complex. Near-normal levels of glucose (HbA_{1c} <7%; <53 mmol/mol) are associated with a decrease in microvascular complications; however, this does not apply to macrovascular complications. Of note, tight glucose control targets may put a patient at risk of hypoglycaemia, which, in turn, is associated with vascular events.[17] Indeed, trials that targeted intensive glycaemic control in patients with T2D collectively failed to demonstrate that lowering HbA_{1c} reduces major adverse CV events (MACE).[18–20] In addition, observational studies indicate there is a U-shaped relationship between HbA_{1c} and clinical outcome, indicating that lower HbA_{1c} is not always better.[21,22]

Therefore, current guidelines recommend avoidance of hypoglycaemia and tight glucose targets of HbA_{1c} <7.0% in individuals with a long life expectancy, while moderate targets <8.5% are recommended for older patients with a short life expectancy.[5]

However, while there is a non-linear relationship between HbA_{1c} targets and CV risk in patients with diabetes, several dedicated CVOTs have demonstrated that new glucose-lowering medications, including GLP-1 RAs and SGLT2Is, reduce CV risk independent of glucose management.[7,23,24]

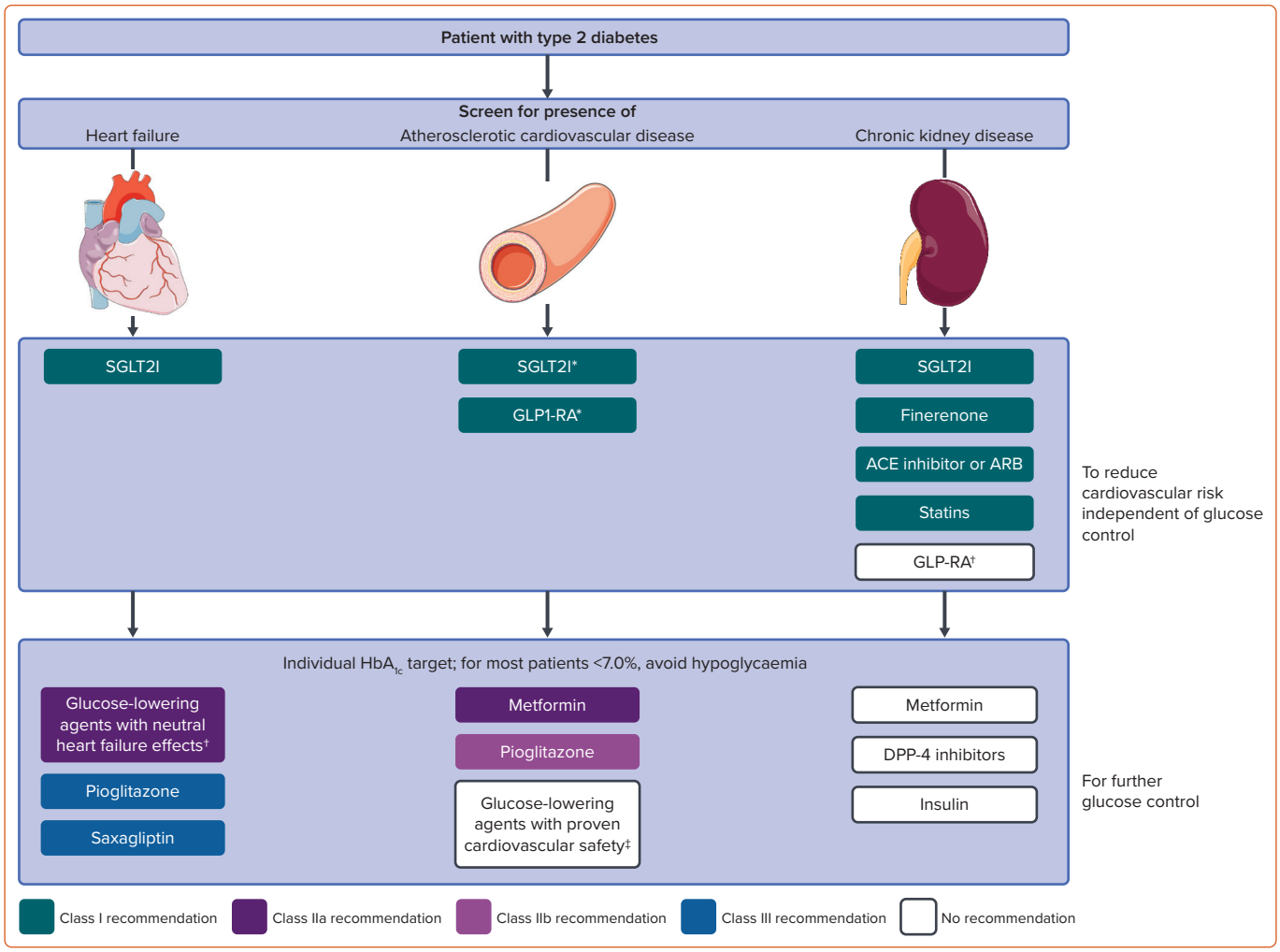
Glucagon-Like Peptide-1 Receptor Agonists

GLP-1 RAs can increase insulin secretion normally triggered by endogenous GLP-1 in response to nutrient ingestion.[25] This process has been described to be impaired in patients with diabetes for reasons that remain unclear.[26]

Eight randomised, placebo-controlled trials have examined the CV safety and efficacy of GLP-1 RAs in patients with T2D and five trials demonstrated superior CV outcomes including CV death, MI and stroke compared to placebo. A recent meta-analysis by Sattar et al. of seven of the eight trials demonstrated that treatment with GLP-1 RAs resulted in a 14% reduction in CV death (HR 0.85; 95% CI [0.78–0.93]), a 12% reduction in MI (HR 0.88 (95% CI [0.81–0.96]), a 19% reduction in stroke (HR 0.81; 95% CI [0.74–0.90]) and 12% reduction in hospitalisation for HF (HR 0.88; 95% CI 0.79–0.98]).[27] Of note, the treatment benefit of GLP-1 RAs was numerically higher in diabetes patients with ASCVD (15% versus 6%) but p for interaction failed to reach statistical significance (p=0.064). However, given the increased absolute risk in patients with ASCVD, a greater risk reduction can be expected.

Based on these results, GLP-1 RAs are among the preferred glucose-lowering strategies in patients with T2D and ASCVD, independent of glucose status (*Figure 2*).[5]

Figure 2: Treatment Algorithm Type 2 Diabetes and Cardiovascular Disease



*Therapeutic strategies presented are according to 2023 European Society of Cardiology guidelines for the management of cardiovascular disease in patients with diabetes.[4] *Independent of HbA_{1c}: only GLP1-RA and SGLT-2 inhibitors with proven CV benefit should be used (i.e. GLP1-RA: raglutide, semaglutide (subcutaneous), dulaglutide, efpeglenatide; SGLT-2I: empagliflozin, canagliflozin, dapagliflozin, sotagliflozin); †no guideline recommendation yet; however, semaglutide reduced the risk of clinically important kidney outcomes and death from cardiovascular cause in patients with type 2 diabetes in the FLOW study.[57] ‡DPP-4 inhibitors (sitagliptin, alogliptin, linagliptin), ertugliflozin, sulfonylureas (glimeperide or gliclazide), insulin glargine, insulin degludec, GLP1-RA (xisenatide, exenatide extended release, oral semaglutide). §GLP1-RA, sitagliptin, linagliptin, metformin, insulin glargine and insulin degludec. ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; DPP-4 = dipeptidyl peptidase-4; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT2I = sodium–glucose co-transporter-2 inhibitor. Created using images from Servier Medical Art. Reproduced under a Creative Commons CC BY 4.0 licence.*

Sodium–Glucose Co-transporter-2 Inhibitors

SGLT2 receptors are located in the proximal tubules of the nephron and increase glucose reabsorption. Inhibition of the SGLT2 receptor leads to increased urinary glucose excretion, and pharmacological inhibition has been used for glucose control.

Seven CVOTs for SGLT2 inhibition have been published and six trials were recently summarised in a meta-analysis that demonstrated a reduction in the primary ASCVD-based composite of CV death, MI or stroke (MACE). This meta-analysis demonstrated a 10% reduction in CV outcomes.[28] This risk reduction was numerically higher in patients with ASCVD compared to patients without ASCVD (11% versus 6%) but failed to reach statistical significance (p=0.63).

In summary, SGLT2Is are a preferred glucose-lowering therapy and may be considered to reduce CV risk, independent of glucose control.

Additional Strategies to Reduce Cardiovascular Risk

The role of comorbidities in diabetes and ASCVD was examined in detail by Rawshani et al., who demonstrated that the risk of acute MI in T2D patients aged <55 years was approximately seven-fold higher (HR 7.69; 95% CI [5.02–11.77]) when five risk factors (HbA_{1c} >7.0%, arterial hypertension, albuminuria, smoking and LDL cholesterol >2.5 mmol/l) were present compared to those without those risk factors.[29] These data indicate that timely identification and treatment of comorbidities in patients with T2D is of utmost importance to improve prognosis.

Data from the Steno-2 study demonstrated that, in patients with advanced T2D and established microalbuminuria, multifactorial therapy (treatment targets: HbA1c <6.5%; total cholesterol <175 mg/dl; and blood pressure <130/80 mmHg) resulted in 50% fewer micro- and macro-vascular events after a 7.8-year follow-up.[30] Therefore, treatment of ASCVD in patients with diabetes needs to be multidisciplinary and address all CV risk factors present (e.g. target systolic blood pressure 130 mmHg and <130 mmHg if tolerated, but not <120 mmHg; LDL cholesterol levels ≤55 mg/dl; aspirin in patients with previous MI or revascularisation).[5]

Heart Failure with Type 2 Diabetes

Diabetes is an important and frequently unrecognised risk factor for HF,

and patients with diabetes have a two- to four-fold increased risk of HF compared to individuals without diabetes.[31]

HF in diabetes may present with reduced, mildly reduced or preserved ejection fraction (HFrEF, HFmrEF or HFpEF, respectively) and evidence for disease-modifying therapy differs based on this prognostic distinction. In addition, patients with HF show an increased prevalence of disturbed glucose metabolism or diabetes; unrecognised HF was present in 28% of a diabetes population identified by a standardised systemic work-up.[32,33]

Given the increased risk of HF in patients with diabetes, systematic screening strategies are recommended to identify patients with HF and diabetes whenever possible.[5]

Heart Failure Risk Reduction with Glucose-lowering Medications

In T2D patients, each 1% rise in HbA_{1c} is associated with an 8% increase in HF risk independent of other CV risk factors, indicating the central role of glucose metabolism in the disease.[34] Therefore, the concept of diabetic cardiomyopathy as independent entity has been described. However, while smaller trials suggest its existence, definitive proof is missing.[35]

Nevertheless, it is established that several mechanisms present in diabetes facilitate myocardial dysfunction including reduced insulin signalling, reduced nitric oxide bioavailability, activation of the renin-angiotensin-aldosterone system by advanced glycation end products and increased collagen deposition.[35] In addition, microvascular dysfunction in diabetes is linked to reduced myocardial perfusion and suggests increased tissue hypoxia as additional mechanisms.[36]

However, despite strong experimental evidence, the link between glucose control and HF events remains unclear. A post hoc analysis of seven randomised controlled trials (RCTs) that tested intensive glucose-lowering regimens compared to standard therapy found no relationship between HF events and glucose lowering.[37]

Therefore, there are no specific HbA1c targets for patients with HF and diabetes, and individual targets are recommended. Nonetheless, in HF, the choice of glucose-lowering medication is critical. While SGLT2Is reduce CV death and hospitalisation for HF, GLP-1 RAs, metformin, insulin glargine and degludec and dipeptidyl peptidase-4 (DPP-4) inhibitors sitagliptin and linagliptin are safe for glucose lowering. In contrast, the DPP-4 inhibitor saxagliptin as well as pioglitazone (a thiazolidinedione) are associated with an increased risk of HF hospitalisation and should be avoided (*Figure 2*).[38–40]

Sodium-glucose Co-transporter–2 Inhibitors

Treatment with SGLT2Is has consistently been demonstrated to reduce HF hospitalisation in all trials of SGLT2Is in patients with T2D.[28] In HFrEF, the beneficial effects of SGLT2Is were confirmed by the DAPA-HF and EMPEROR-reduced trials for dapagliflozin and empagliflozin, respectively.[41,42] A meta-analysis demonstrated that SGLT2 inhibition in patients with HF led to a 13% reduction in all-cause mortality (HR 0.87 (95% CI [0.77–0.98]) and 26% reduction in hospitalisation for HF (HR 0.74 (95% CI [0.68–0.82]). Of note, both trials included patients with and without T2D; however, these results were independent of diabetes status (p for heterogeneity=0.65).[43]

In HFpEF, a recent meta-analysis of 12,251 participants from the DELIVER and EMPEROR-Preserved trials showed a reduction in the composite of CV death (HR 0.80; 95% CI [0.77–1.00]) and first hospitalisation for HF (HR 0.74; 95% CI [0.67–0.83]). This treatment effect was independent of left ventricular function and therefore SGLT2 inhibition is now considered a class 1 recommendation across the entire spectrum of left ventricular ejection fraction in HF.[5]

Glucagon-like Peptide-1 Receptor Agonists

The role of GLP-1 RAs in the context of HFrEF and diabetes is inconclusive. Two small RCTs indicate that GLP-1 RAs in HFrEF deserve further attention since these trials demonstrated a numerical increase in cardiac events (LIVE trial: 10.0 versus 3.0%; p=0.04) and HF hospitalisation (FIGHT trial: HR 1.3; 95% CI [0.92–1.83]).[44,45] However, these trials enrolled relatively few patients and were unpowered for the above-mentioned endpoints so conclusive evidence is unavailable.

However, it needs to be underlined that eight large CVOTs did not show signs of harm in patients with HF and diabetes so GLP-1 RAs are considered safe for additional glucose control in patients with HF.[5,46]

Additional Strategies to Reduce Risk of Heart Failure and Type 2 Diabetes

Patients with T2D and HFrEF benefit in the same way from guideline-directed medical therapy (GDMT) as patients without T2D. In addition, given the increased absolute risk with HF, patients with T2D may benefit even more from GDMT. Therefore, in HFrEF, the following should be prescribed when the disease is identified and whenever possible: angiotensin receptor neprilysin inhibition or angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers; mineralocorticoid receptor antagonism (excluding finerenone); and β-blockers.[5,47]

Additional treatment by ivabradine in patients in sinus rhythm with a persistent heart rate of ≥70 BPM taking β-blockers reduced CV endpoints and HF hospitalisation, irrespective of HF status.[48] Diuretics should be added for symptom relief and decongestion.[49]

In patients with HFmrEF, evidence for GDMT is mainly derived from subgroup analysis of HFrEF trials and therefore prospective trials are needed.[47]

In patients with HFpEF and diabetes, there is no evidence of benefit of GDMT beyond treatment with an SGLT2I.[50]

Chronic Kidney Disease with Type 2 Diabetes

CKD is defined as abnormalities of kidney structure or function that are present for a minimum of 3 months.[51] It is classified based on cause, eGFR and albuminuria.[52] Hyperglycaemia is strongly associated with CKD, and diabetic kidney disease (DKD) develops in nearly 50% of patients with T2D, underlining the relationship between diabetes and CKD.[52,53] DKD is the leading cause of kidney failure globally, requiring kidney transplantation or dialysis.[54] The leading cause of death in patients with DKD is CVD, which underlines the importance of therapeutic strategies that address progression of kidney failure and CVD risk. Therefore, it is recommended that patients with diabetes are routinely screened for presence of kidney disease by assessing eGFR (CKD-EPI) and UACR.[5]

Cardiovascular and Kidney Risk Reduction by Glucose-Lowering Agents

Research indicates a complex interplay of hyperglycaemia, inflammation and oxidative stress induces irreversible changes in the nephron, leading to functional deterioration (decrease in eGFR) and structural deterioration

(albuminuria).[55] In a large meta-analysis, the effect of intensive glucose control with a tight HbA1c target <7.0 % demonstrated a protective effect on diabetic nephropathy indicated by a reduction in albuminuria while other endpoints, including renal death and end-stage kidney disease, remained unaffected, which implies a more complex relationship.[56] This relationship is further complicated by the fact that the correlation between HbA1c and glucose levels is diminished in CKD due to the coexistent presence of renal anaemia.[57] Nevertheless, current guidelines recommend an individualised HbA1c target of 6.5–8.0% for patients with diabetes and CKD with targets <7.0% to prevent microvascular complications whenever possible.[5]

Glucagon-like Peptide-1 Receptor Agonists

A meta-analysis examining GLP-1 RAs demonstrated that some GLP-1 RAs show favourably lower outcomes of albuminuria in patients with diabetes while their effect on disease progression was less clear and deserves further attention in future trials.[27]

This remaining question was recently addressed in the FLOW trial that tested the role of 1.0 mg semaglutide once weekly by subcutaneous injection on disease progression in patients with mild to advanced CKD. In 3,533 participants, semaglutide led to a 24% risk reduction in kidney failure (i.e. dialysis; kidney-transplantation or eGFR <15 ml/min/1.73 m^2; ≥50% reduction in eGFR; or kidney-related or CV-related death).[58]

In addition, semaglutide treatment reduced MACE by 18% (HR 0.82; 95% CI [0.68–0.98]), CV mortality by 29% (HR 0.71; 95% CI [0.56–0.89]) and all-cause mortality by 20% (HR 0.80; 95% CI [0.67–0.95]). Subgroup analysis revealed a uniform effect across the spectrum of diabetes duration, glucose control and eGFR, even in patients with an HbA_{1c} ≤7.0 % and an eGFR ≥60 ml/min 1.73 m^2, indicating that early initiation of the GLP-1 RA may prevent outcomes.[58]

While there was no clear heterogeneity, patients on SGLT2Is benefited less from GLP-1 RA, an observation that deserves further attention in the future.[58]

Sodium–Glucose Co-transporter-2 Inhibitors

A recent meta-analysis of all large SGLT2I trials assessed the role of SGLT2Is on kidney function. It was demonstrated that SGLT2 inhibition led to a 37% decrease in kidney disease progression (RR 0.63; 95% CI [0.58–0.69]) and a 23% decrease in acute kidney injury (RR 0.77; CI [0.70–0.84]).[59] In addition, SGLT2Is reduced CV mortality risk by 14% (RR 0.86; 95% CI [0.81–0.92]).[59] Therefore, initiation of SGLT2Is tested in CKD (i.e. canagliflozin, empagliflozin or dapagliflozin) is recommended in all CKD patients by European Society of Cardiology and American Heart Association AHA guidelines.

Glucose-independent Strategies in Chronic Kidney Disease and Type 2 Diabetes

Glucose-independent therapeutic strategies in CKD have two targets: to reduce kidney disease progression; and to reduce CVD risk. CVD treatment strategies in patients with DKD are similar to those for patients without CKD; however, in DKD, intensive LDL cholesterol lowering, even in the absence of ASCVD and a blood pressure target of ≤130/80 mmHg, is recommended.[5] Nevertheless, none of these treatments have demonstrated to halt decline in kidney function with the exception of the new non-steroidal mineralocorticoid receptor finerenone and angiotensin-converting enzyme (ACE) inhibition.

Selective, Non-steroidal Mineralocorticoid Receptor Antagonists

Mineralocorticoid receptor antagonism has been demonstrated to reduce blood pressure and albuminuria in patients with CKD.[60] However, due to the parallel risk of hyperkalaemia, this therapeutic strategy is limited in patients with CKD.

The novel non-steroidal mineralocorticoid receptor antagonist finerenone is highly selective for the mineralocorticoid receptor and therefore has fewer side effects, making mineralocorticoid receptor antagonism suitable for patients with advanced CKD. Finerenone has been tested in two dedicated outcome trials in patients with CKD and T2D, both of which demonstrated that the drug reduces the risk of kidney failure and CV events compared to placebo.

In the prespecified, pooled analysis of both trials, the risk of the composite kidney endpoint (kidney failure; sustained decrease in eGFR ≥57% over 4 weeks; and renal death) was reduced by 23% (HR 0.77; 95% CI [0.67–0.88]). In addition, the composite CV endpoint (CV death, non-fatal MI, non-fatal stroke and hospitalisation for HF) was reduced by 14% (HR 0.86; 95% CI [0.78–0.95]), driven mainly by a reduced number of hospitalisations for HF. Patients with HFrEF were excluded from the study, indicating a potential role of this therapy in patients with HFpEF or new-onset HF.

Based on these results, finerenone is now recommended in all patients with diabetes and CKD with an eGFR ≥25 ml/min/1.73m^2 and signs of albuminuria (i.e. UACR ≥3 mg/mmol for eGFR 25–60 ml/min; UACR ≥30 mg/mmol for eGFR >60 ml/min/1.73m^2).

Angiotensin-converting Enzyme Inhibitors/ Angiotensin-receptor Blockers

ACE inhibitors (e.g. captopril) and angiotensin-receptor blockers (e.g. irbesartan/losartan) have been demonstrated in dedicated outcome trials to slow down CKD progression with a reduction in end-stage renal disease compared to placebo.[61,62] In addition, irbesartan and losartan slow down the progression from microalbuminuria to overt nephropathy.[63,64] ACE inhibitors should not be withheld from patients out of fear of further CKD deterioration.[65]

Conclusion

Given the elevated risks of patients with diabetes and CVD and/or CKD and given the overwhelming evidence from large CVOTs in T2D, early initiation of GDMT is crucial. From a cardiologist perspective, systemic screening strategies for ASCVD, HF and CKD (measuring eGFR and UACR) are essential in all patients with T2D; conversely, screening for diabetes needs to be performed in all patients with CVD to allow timely identification of this condition.

Once these comorbidities are identified, it is essential that treatment with CV risk-reducing therapies, such as SGLT2Is (in patients with T2D and ASCVD, HF or CKD), GLP-1 RAs (in patients with T2D and ASCVD) and finerenone (in patients with T2D and CKD), are rapidly implemented on top of standard of care and cardiologists nowadays have a leading role in this interdisciplinary task. ❑

1. Emerging Risk Factors Collaboration, Sarwar N, Gao P, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010;375:2215–22. https://doi.org/10.1016/S0140-6736(10)60484-9; PMID: 20609967.
2. Ke C, Narayan KMV, Chan JCN, et al. Pathophysiology, phenotypes and management of type 2 diabetes mellitus in Indian and Chinese populations. *Nat Rev Endocrinol* 2022;18:413–32. https://doi.org/10.1038/s41574-022-00669-4; PMID: 35508700.
3. Diabetes Atlas 2021. https://diabetesatlas.org/ (accessed 8 January 2024).
4. Jankowski J, Floege J, Fliser D, et al. Cardiovascular disease in chronic kidney disease: pathophysiological insights and therapeutic options. *Circulation* 2021;143:1157–72. https://doi.org/10.1161/CIRCULATIONAHA.120.050686; PMID: 33720773.
5. Marx N, Federici M, Schutt K, et al. 2023 ESC guidelines for the management of cardiovascular disease in patients with diabetes. *Eur Heart J* 2023;44:4043–140. https://doi.org/10.1093/eurheartj/ehad192; PMID: 37622663.
6. Agarwal R, Filippatos G, Pitt B, et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. *Eur Heart J* 2022;43:474–84. https://doi.org/10.1093/eurheartj/ehab777; PMID: 35023547.
7. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117–28. https://doi.org/10.1056/NEJMoa1504720; PMID: 26378978.
8. Clerc OF, Fuchs TA, Stehli J, et al. Non-invasive screening for coronary artery disease in asymptomatic diabetic patients: a systematic review and meta-analysis of randomised controlled trials. *Eur Heart J Cardiovasc Imaging* 2018;19:838–46. https://doi.org/10.1093/ehjci/jey014; PMID: 29452348.
9. Anand DV, Lim E, Hopkins D, et al. Risk stratification in uncomplicated type 2 diabetes: prospective evaluation of the combined use of coronary artery calcium imaging and selective myocardial perfusion scintigraphy. *Eur Heart J* 2006;27:713–21. https://doi.org/10.1093/eurheartj/ehi808; PMID: 16497686.
10. Vrints C, Andreotti F, Koskinas KC, et al. 2024 ESC guidelines for the management of chronic coronary syndromes. *Eur Heart J* 2024;45:3415–537. https://doi.org/10.1093/eurheartj/ehae177; PMID: 39210710.
11. Zhou M, Liu J, Hao Y, et al. Prevalence and in-hospital outcomes of diabetes among patients with acute coronary syndrome in China: findings from the Improving Care for Cardiovascular Disease in China-Acute Coronary Syndrome Project. *Cardiovasc Diabetol* 2018;17:147. https://doi.org/10.1186/s12933-018-0793-x; PMID: 30482187.
12. Dunlay SM, Givertz MM, Aguilar D, et al. Type 2 diabetes mellitus and heart failure: a scientific statement from the American Heart Association and the Heart Failure Society of America: this statement does not represent an update of the 2017 ACC/AHA/HFSA heart failure guideline update. *Circulation* 2019;140:e294–324. https://doi.org/10.1161/CIR.0000000000000691; PMID: 31167558.
13. Fox CS, Matsushita K, Woodward M, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet* 2012;380:1662–73. https://doi.org/10.1016/S0140-6736(12)61350-6; PMID: 23013602.
14. Rawshani A, Rawshani A, Franzen S, et al. Mortality and cardiovascular disease in type 1 and type 2 diabetes. *N Engl J Med* 2017;376:1407–18. https://doi.org/10.1056/NEJMoa1608664; PMID: 28402770.
15. Haffner SM, Lehto S, Ronnemaa T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998;339:229–34. https://doi.org/10.1056/NEJM199807233390404; PMID: 9673301.
16. Chait A, Eckel RH, Vrablik M, Zambon A. Lipid-lowering in diabetes: an update. *Atherosclerosis* 2024;394:117313. https://doi.org/10.1016/j.atherosclerosis.2023.117313; PMID: 37945448.
17. International Hypoglycaemia Study Group. Hypoglycaemia, cardiovascular disease, and mortality in diabetes: epidemiology, pathogenesis, and management. *Lancet Diabetes Endocrinol* 2019;7:385–96. https://doi.org/10.1016/S2213-8587(18)30315-2; PMID: 30926258.
18. ACCORD Study Group, Buse JB, Bigger JT, et al. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: design and methods. *Am J Cardiol* 2007;99:21i–33i. https://doi.org/10.1016/j.amjcard.2007.03.003; PMID: 17599422.
19. Agrawal L, Azad N, Emanuele NV, et al. Observation on renal outcomes in the Veterans Affairs Diabetes Trial. *Diabetes Care* 2011;34:2090–4. https://doi.org/10.2337/dc11-0175; PMID: 21775749.
20. ADVANCE Collaborative Group, Patel A, MacMahon S, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560–72. https://doi.org/10.1056/NEJMoa0802987; PMID: 18539916.
21. Currie CJ, Peters JR, Tynan A, et al. Survival as a function of HbA_{1c} in people with type 2 diabetes: a retrospective cohort study. *Lancet* 2010;375:481–9. https://doi.org/10.1016/S0140-6736(09)61969-3; PMID: 20110121.
22. Zoungas S, Chalmers J, Ninomiya T, et al. Association of HbA_{1c} levels with vascular complications and death in patients with type 2 diabetes: evidence of glycaemic thresholds. *Diabetologia* 2012;55:636–43. https://doi.org/10.1007/s00125-011-2404-1; PMID: 22186981.
23. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;375:1834–44. https://doi.org/10.1056/NEJMoa1607141; PMID: 27633186.
24. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;375:311–22. https://doi.org/10.1056/NEJMoa1603827; PMID: 27295427.
25. Davidson MH. Cardiovascular effects of glucagonlike peptide-1 agonists. *Am J Cardiol* 2011;108(3 Suppl):33B–41. https://doi.org/10.1016/j.amjcard.2011.03.046; PMID: 21802579.
26. Calanna S, Christensen M, Holst JJ, et al. Secretion of glucagon-like peptide-1 in patients with type 2 diabetes mellitus: systematic review and meta-analyses of clinical studies. *Diabetologia* 2013;56:965–72. https://doi.org/10.1007/s00125-013-2841-0; PMID: 23377698.
27. Sattar N, Lee MMY, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol* 2021;9:653–62. https://doi.org/10.1016/S2213-8587(21)00203-5; PMID: 34425083.
28. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. *JAMA Cardiol* 2021;6:148–58. https://doi.org/10.1001/jamacardio.2020.4511; PMID: 33031522.
29. Rawshani A, Rawshani A, Franzen S, et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2018;379:633–44. https://doi.org/10.1056/NEJMoa1800256; PMID: 30110583.
30. Oellgaard J, Gaede P, Rossing P, et al. Reduced risk of heart failure with intensified multifactorial intervention in individuals with type 2 diabetes and microalbuminuria: 21 years of follow-up in the randomised Steno-2 study. *Diabetologia* 2018;61:1724–33. https://doi.org/10.1007/s00125-018-4642-y; PMID: 29850922.
31. Nichols GA, Gullion CM, Koro CE, et al. The incidence of congestive heart failure in type 2 diabetes: an update. *Diabetes Care* 2004;27:1879–84. https://doi.org/10.2337/diacare.27.8.1879; PMID: 15277411.
32. Gottdiener JS, Arnold AM, Aurigemma GP, et al. Predictors of congestive heart failure in the elderly: the cardiovascular health study. *J Am Coll Cardiol* 2000;35:1628–37. https://doi.org/10.1016/s0735-1097(00)00582-9; PMID: 10807470.
33. Boonman-de Winter LJ, Rutten FH, Cramer MJ, et al. High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type 2 diabetes. *Diabetologia* 2012;55:2154–62. https://doi.org/10.1007/s00125-012-2579-0; PMID: 22618812.
34. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;321:405–12. https://doi.org/10.1136/bmj.321.7258.405; PMID: 10938048.
35. Jia G, Hill MA, Sowers JR. Diabetic cardiomyopathy: an update of mechanisms contributing to this clinical entity. *Circ Res* 2018;122:624–38. https://doi.org/10.1161/CIRCRESAHA.117.311586; PMID: 29449364.
36. Kenny HC, Abel ED. Heart failure in type 2 diabetes mellitus. *Circ Res* 2019;124:121–41. https://doi.org/10.1161/CIRCRESAHA.118.311371; PMID: 30605420.
37. Castagno D, Baird-Gunning J, Jhund PS, et al. Intensive glycemic control has no impact on the risk of heart failure in type 2 diabetic patients: evidence from a 37,229 patient meta-analysis. *Am Heart J* 2011;162:938–48.e2. https://doi.org/10.1016/j.ahj.2011.07.030; PMID: 22093212.
38. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* 2009;373:2125–35. https://doi.org/10.1016/S0140-6736(09)60953-3; PMID: 19501900.
39. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 2006;368:1096–105. https://doi.org/10.1016/S0140-6736(06)69420-8; PMID: 16997664.
40. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013;369:1317–26. https://doi.org/10.1056/NEJMoa1307684; PMID: 23992601.
41. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;381:1995–2008. https://doi.org/10.1056/NEJMoa1911303; PMID: 31535829.
42. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;383:1413–24. https://doi.org/10.1056/NEJMoa2022190; PMID: 32865377.
43. Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet* 2020;396:819–29. https://doi.org/10.1016/S0140-6736(20)31824-9; PMID: 32877652.
44. Jorsal A, Kistorp C, Holmager P, et al. Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE) – a multicentre, double-blind, randomised, placebo-controlled trial. *Eur J Heart Fail* 2017;19:69–77. https://doi.org/10.1002/ejhf.657; PMID: 27790809.
45. Sharma A, Ambrosy AP, DeVore AD, et al. Liraglutide and weight loss among patients with advanced heart failure and a reduced ejection fraction: insights from the FIGHT trial. *ESC Heart Fail* 2018;5:1035–43. https://doi.org/10.1002/ehf2.12334; PMID: 30120812.
46. Khan MS, Fonarow GC, McGuire DK, et al. Glucagon-like peptide 1 receptor agonists and heart failure: the need for further evidence generation and practice guidelines optimization. *Circulation* 2020;142:1205–18. https://doi.org/10.1161/CIRCULATIONAHA.120.045888; PMID: 32955939.
47. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;42:3599–726. https://doi.org/10.1093/eurheartj/ehab368; PMID: 34447992.
48. Komajda M, Tavazzi L, Francq BG, et al. Efficacy and safety of ivabradine in patients with chronic systolic heart failure and diabetes: an analysis from the SHIFT trial. *Eur J Heart Fail* 2015;17:1294–301. https://doi.org/10.1002/ejhf.347; PMID: 26377342.
49. Faris R, Flather M, Purcell H, et al. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. *Int J Cardiol* 2002;82:149–58. https://doi.org/10.1016/s0167-5273(01)00600-3; PMID: 11853901.
50. McDonagh TA, Metra M, Adamo M, et al. 2023 focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2023;44:3627–39. https://doi.org/10.1093/eurheartj/ehad195; PMID: 37622666.
51. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int* 2024;105:S117–314. https://doi.org/10.1016/j.kint.2023.10.018; PMID: 38490803.
52. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int* 2022;102:S1–127. https://doi.org/10.1016/j.kint.2022.06.008; PMID: 36272764.
53. Gheith O, Farouk N, Nampoory N, et al. Diabetic kidney disease: world wide difference of prevalence and risk factors. *J Nephropharmacol* 2016;5:49–56. PMID: 28197499.
54. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease study 2017. *Lancet* 2020;395:709–33. https://doi.org/10.1016/S0140-6736(20)30045-3; PMID: 32061315.
55. Jung CY, Yoo TH. Pathophysiologic mechanisms and potential biomarkers in diabetic kidney disease. *Diabetes Metab J* 2022;46:181–97. https://doi.org/10.4093/dmj.2021.0329; PMID: 35385633.
56. Zoungas S, Arima H, Gerstein HC, et al. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. *Lancet Diabetes Endocrinol* 2017;5:431–7. https://doi.org/10.1016/S2213-8587(17)30104-3; PMID: 28365411.
57. Jung M, Warren B, Grams M, et al. Performance of non-traditional hyperglycemia biomarkers by chronic kidney disease status in older adults with diabetes: results from the Atherosclerosis Risk In Communities study. *J Diabetes*

2018;10:276–85. https://doi.org/10.1111/1753-0407.12618; PMID: 29055090.
58. Perkovic V, Tuttle KR, Rossing P, et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. *N Engl J Med* 2024;391:109–21. https://doi.org/10.1056/NEJMoa2403347; PMID: 38785209.
59. Nuffield Department of Population Health Renal Studies Group, SGLT2 Inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet* 2022;400:1788–801. https://doi.org/10.1016/S0140-6736(22)02074-8; PMID: 36351458.
60. Currie G, Taylor AHM, Fujita T, et al. Effect of mineralocorticoid receptor antagonists on proteinuria and progression of chronic kidney disease: a systematic review and meta-analysis. *BMC Nephrol* 2016;17:127. https://doi.org/10.1186/s12882-016-0337-0; PMID: 27609359.
61. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993;329:1456–62. https://doi.org/10.1056/NEJM199311113292004; PMID: 8413456.
62. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;345:861–9. https://doi.org/10.1056/NEJMoa011161; PMID: 11565518.
63. Parving HH, Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001;345:870–8. https://doi.org/10.1056/NEJMoa011489; PMID: 11565519.
64. Makino H, Haneda M, Babazono T, et al. Prevention of transition from incipient to overt nephropathy with telmisartan in patients with type 2 diabetes. *Diabetes Care* 2007;30:1577–8. https://doi.org/10.2337/dc06-1998; PMID: 17389334.
65. Bhandari S, Mehta S, Khwaja A, et al. Renin-angiotensin system inhibition in advanced chronic kidney disease. *N Engl J Med* 2022;387:2021–32. https://doi.org/10.1056/NEJMoa2210639; PMID: 36326117.