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Special article

Clinical Practice Guideline for detection and management of diabetic kidney disease: A consensus report by the Spanish Society of Nephrology

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ABSTRACT

To address all the changes in the management of people with diabetes (DM) and chronic kidney disease (CKD), under the auspices of the Spanish Society of Nephrology (SEN), the Spanish Diabetic Nephropathy Study Group (GEENDIAB) decided to publish an updated Clinical Practice Guideline for detection and management of diabetic kidney disease (DKD). It is aimed at a wide audience of clinicians treating diabetes and CKD. The terminology of kidney disease in diabetic patients has evolved toward a more inclusive nomenclature that avoids underdiagnosis of this entity. Thus, the terms "diabetes and kidney disease" and "diabetic kidney disease" are those proposed in the latest KDIGO 2022 guidelines to designate the whole spectrum of patients who can benefit from a comprehensive therapeutic approach only differentiated according to eGFR range and albuminuria.

Recommendations have been divided into five main areas of interest: Chapter 1: Screening and diagnosis of diabetic kidney disease, Chapter 2: Metabolic control in people with diabetes and CKD, Chapter 3: Blood pressure control in people with diabetic kidney disease, Chapter 4: Treatment targeting progression of CKD in people with diabetic kidney disease, and Chapter 5: Antiplatelet or anticoagulant therapy in people with diabetes and CKD.

World Health Organization (WHO) recommendations for guideline development were followed to report this guideline. Systematic reviews were carried out, with outcome ratings and summaries of findings, and we reported the strength of recommendations following the "Grading of Recommendations Assessment, Development and Evaluation" GRADE evidence profiles.

Guía de práctica clínica sobre detección y manejo de la enfermedad renal diabética: documento de consenso de la Sociedad Española de Nefrología

Palabras clave:
Diabetes mellitus
Guías de práctica clínica
Enfermedades renales diabéticas
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RESUMEN

Para abordar todas las novedades en el manejo de las personas con diabetes (DM) y enfermedad renal crónica (ERC), el Grupo Español de Estudio de Nefropatía Diabética (GEENDIAB), bajo los auspicios de la Sociedad Española de Nefrología (SEN), ha decidido publicar una Actualización de la Guía de Práctica Clínica para la detección y el manejo de la ERC, dirigida a una amplia audiencia de clínicos que tratan la diabetes y la ERC. La terminología de la enfermedad renal en los pacientes diabéticos ha evolucionado hacia una nomenclatura más inclusiva que evita el infradiagnóstico de esta entidad. Así, los términos «diabetes y enfermedad renal» y «enfermedad renal diabética» son los propuestos en las últimas guías KDIGO 2022 para designar a todo el espectro de pacientes que pueden beneficiarse de un abordaje terapéutico integral, solo diferenciado según el rango de la FGe y la albuminuria.

Las recomendaciones se han dividido en 5 áreas principales de interés: Capítulo 1: Cribado y diagnóstico de la enfermedad renal diabética; Capítulo 2: Control metabólico en personas con diabetes y ERC; Capítulo 3: Control de la presión arterial en personas con enfermedad renal diabética; Capítulo 4: Tratamiento dirigido a la progresión de la ERC en personas con enfermedad renal diabética y Capítulo 5: Tratamiento antiagregante plaquetario o anticoagulante en personas con diabetes y ERC.

Para elaborar esta guía se siguieron las recomendaciones de la Organización Mundial de la Salud (OMS) para el desarrollo de guías. Se realizaron revisiones sistemáticas, con evaluación de los resultados y resúmenes de los hallazgos, y se informó de la fuerza de las recomendaciones siguiendo los perfiles de evidencia Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Executive summary

Chapter 1: Screening and diagnosis of diabetic kidney disease

Recommendation 1.1. Annual screening is recommended for the detection of diabetic kidney disease. In type 1 diabetes (T1D), this should start five years after the diagnosis of diabetes, and in type 2 diabetes (T2D) or latent autoimmune diabetes in adults (LADA), from the moment the disease is detected. Measurement of the presence of albuminuria (evaluating urine albumin-to-creatinine ratio of a random urine sample) and evaluation of estimated glomerular filtration rate (eGFR) using CKD-EPI formulae would be recommendable (2D).

Recommendation 1.2. Referring people with diabetes to a nephrologist may be appropriate in any situation where a physician needs assistance in managing diabetic kidney disease according to current recommendations (2D).

Recommendation 1.3. Performing a kidney biopsy on people with diabetes should be indicated in the following situations: (1) when there is a rapid increase in proteinuria or nephrotic range proteinuria, (2) proteinuria > 1 g/day in 24 h urine collection in diabetes with under five years of progress, (3) deterioration of kidney function with and without diabetic retinopathy, (4) alterations in the urinary sediment (dysmorphic red blood cells) not associated with an infectious process (urinary infection), (5) rapid decrease in glomerular filtration rate in patients with previous stable kidney function or (6) clinical and/or analytical signs of associated immune disease (2D).

Chapter 2: Metabolic control in people with diabetes and CKD

Recommendation 2.1. Patients with T2D and CKD should be treated with a sodium-glucose cotransporter-2 inhibitor and, if necessary, additional pharmacological treatment should be introduced to improve glycemic control (1B).

Recommendation 2.2. Glucagon-like peptide-1 receptor agonists are recommended as additional pharmacological treatment, as they have proven cardiovascular benefit and, recently, kidney benefit in terms of CKD progression in people with T2D (1B).

Chapter 3: Blood pressure control in people with diabetic kidney disease

Recommendation 3.1. We recommend blood pressure control with a target systolic blood pressure (SBP) of <130 mm Hg, when tolerated, in patients with diabetic kidney disease. Otherwise, a general target of SBP < 140 is recommended (2C).

Recommendation 3.2. We recommend starting angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) for patients with either hypertension or diabetic kidney disease (2B).

Recommendation 3.3. Steroidal mineralocorticoid receptor antagonists (MRA) are probably useful for managing hypertension in patients with eGFR > 30 ml/min/1.73 m^2 and serum potassium < 4.8 mmol/L (2D).

Recommendation 3.4. Although nonsteroidal MRA may be helpful in blood pressure control, we do not recommend them for blood pressure management due to the current lack of evidence (2B).

Recommendation 3.5. The combination of ACEi with ARB or aliskiren therapy in patients with diabetes and CKD should be avoided (2D).

Chapter 4: Treatment targeting progression of CKD in people with diabetic kidney disease

Recommendation 4.1. Patients with T2D and CKD with an eGFR ≥20 ml/min/1.73 m^2 should be treated with a sodium-glucose cotransporter-2 inhibitor and continue until end-stage kidney disease (dialysis or kidney transplant) (1A).

Recommendation 4.2. We recommend that treatment with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) should be initiated in patients with diabetes, hypertension, and albuminuria. These medications should be titrated to the highest approved tolerated dose (1A).

Recommendation 4.3. Patients with T2D, eGFR ≥ 25 ml/min/1.73 m^2, and increased albuminuria (uACR > 100 mg/g) on a stable maximal tolerated dose of RAS inhibitors should be treated with a GLP1RA with proven kidney benefit (1A).

Recommendation 4.4. We suggest initiating a nonsteroidal mineralocorticoid receptor antagonist (MRA) with proven kidney and/or cardiovascular benefit for patients with T2D, eGFR ≥25 ml/min/1.73 m^2, normal serum potassium concentration, and albuminuria (uACR ≥ 30 mg/g) despite the maximum tolerated dose of renin–angiotensin system (RAS) inhibitor (1B).

Recommendation 4.5. We suggest maintaining a protein intake of 0.6–0.8 g/kg (weight)/day for patients with diabetes and CKD not treated with dialysis (2C).

Chapter 5: Antiplatelet or anticoagulant therapy in people with diabetes and CKD

Recommendation 5.1. Patients with T1D or T2D and chronic kidney disease with established atherosclerotic cardiovascular disease should be treated with low-dose aspirin (75–100 mg/day) for secondary prevention (1B).

Recommendation 5.2. Dual antiplatelet therapy (with low-dose aspirin and a $P2Y_{12}$ inhibitor) is recommended after acute coronary syndrome or percutaneous coronary intervention, followed by single antiplatelet therapy with a duration determined by a multidisciplinary team based on the benefit-risk profile (1B).

Recommendation 5.3. In patients with T1D or T2D and CKD and a previous non-cardioembolic ischemic stroke or transient ischemic stroke, the long-term use of antiplatelet therapy to reduce the risk of recurrent stroke is recommended (1C).

Recommendation 5.4. Dual antiplatelet therapy (with low-dose aspirin and a $P2Y_{12}$ inhibitor) after acute non-cardioembolic ischemic stroke/transient ischemic attack in patients with T1D or T2D and CKD followed by single antiplatelet therapy should be considered (2C).

Recommendation 5.5. There is no clear evidence of a favorable benefit-risk profile of low-dose aspirin for primary prevention of atherosclerotic cardiovascular disease in patients with T1D or T2D and CKD stage 3 or higher to recommend its prescription (2C).

Recommendation 5.6. Patients with T1D or T2D and CKD with non-valvular atrial fibrillation should preferably be treated with direct oral anticoagulants versus vitamin K antagonists in patients with CKD stages 1–4 (dabigatran up to stage 3b) (1B).

Recommendation 5.7. Patients with T1D or T2D and CKD with venous thromboembolism should preferably be treated with direct oral anticoagulants over vitamin K antagonists in patients with CKD stages 1–4 (dabigatran up to stage 3b) (2C).

Methods for guideline development

The consensus development process was governed by the Spanish Diabetic Nephropathy Study Group (GEENDIAB) under the auspices of the Spanish Society of Nephrology (SEN).

These guidelines adhered to World Health Organization (WHO) recommendations for guideline development (Appendix 1, Suppl. Materials)[1] and have been reported in accordance with the Appraisal of Guidelines for Research and Evaluation (AGREE) II reporting checklist.[2]

The phases of execution of the guidelines were as follows:

1. *Defining the scope of the guideline*. The key guideline questions were asked using the Population, Intervention, Comparator and Outcome (PICO) methodology (Table 1).
2. *Defining the steering committee*. A topic-specific steering committee was selected, consisting of experts including nephrologists and endocrinologists in the topic area, members of the Spanish Diabetic Nephropathy Study Group (GEENDIAB) and two methodologists.
3. *Implementing literature search strategies focused on each of the PICO questions*. Relevant studies were obtained from a systematic literature search. We searched MEDLINE and CENTRAL (Cochrane Central Register of Controlled Trials) until July 2023 (Appendix 2, Suppl. Materials).
4. *Selecting studies according to predefined inclusion criteria*. For Chapter 1, selection was not limited to randomized clinical trials but also included studies that used a pre/post or case-control design, prospective and retrospective studies (cohorts or registry), and systematic reviews and guidelines from other societies. For the remaining chapters, only randomized controlled trials (RCTs) including people with diabetes and chronic kidney disease were included. Reviews and meta-analyses were included for hand-searching of bibliographies for additional literature.
5. *Conducting data extraction and critical appraisal of the literature*. Standard data extraction forms were used to extract data. For randomized controlled trials, risk of bias was assessed using the Cochrane Risk of Bias assessment tool[3] and for observational studies the ROBINS-I tool was used.[4]
6. Perform the evidence synthesis and meta-analysis of included studies. Explored outcomes were: all-cause mortality, cardiovascular mortality, death from kidney causes, individual cardiovascular events (myocardial infarction, stroke, heart failure), need for initiation of RRT, doubling of serum creatinine, new onset of albuminuria > 300 mg/g, kidney composite, major adverse cardiovascular events, heart failure, myocardial infarction, stroke, treatment dropouts due to adverse effects, serious adverse effects, hyperkalemia, glycated hemoglobin (HbA1c) (%), eGFR, % change from baseline uACR, diabetic retinopathy progression, diabetic ketoacidosis, urinary tract infections, gastrointestinal adverse effects, hypoglycemia, amputations, fractures.

Outcome analyses were performed including all RCTs. For dichotomous outcomes, results were expressed as risk ratios (RR) with 95% confidence intervals (CI). Where continuous measurement scales were used to assess treatment effects, the mean difference (MD) was used. We approached time-to-event outcomes as continuous variables. For counts and rates, the results of a study were expressed as a RR, and the (natural) logarithms of the rate ratios were combined across studies using the generic inverse variance method. Data were pooled using the random-effects model.

Multiple intervention group studies were analyzed with different methods: (1) using only the groups with the intervention of interest to create a single pair-wise comparison (if there were three groups including different induction therapies, only one induction therapy was included) and (2) including each pair-wise comparison separately, but with shared intervention groups approximately divided out evenly among the

Table 1 – Clinical questions and systematic review topics in the PICO format.

Guideline Chapter 1	Screening and diagnosis of diabetic kidney disease
Clinical question	How and when is it recommended to screen for kidney disease in people with diabetes?
Clinical question	What are the criteria for referring people with diabetes to a nephrologist?
Clinical question	When is a kidney biopsy indicated in people with diabetes and kidney disease?
Population	Adults with CKD (G1–G5, G5D) and diabetes (T1D and T2D)
Study design	RCT, studies that used a pre/post or case-control design, prospective and retrospective studies (cohorts or registry), and systematic reviews and guidelines from other societies
Guideline Chapter 2	Metabolic control in people with diabetes and CKD
Clinical question	In patients with T1D or T2D and CKD, what are the effects of glucose-lowering medication on clinically relevant outcomes and clinically relevant harms?
Population	Adults with CKD (G1–G5, G5D, G1T–G5T) and diabetes (T1D or T2D)
Intervention	Older therapies—metformin, sulfonylureas, or thiazolidinediones More recent therapies—alpha-glucosidase inhibitors, GLP-1 RA, DPP-4 inhibitors, SGLT2i In T1D: different types of insulin
Comparator	Standard of care/placebo
Outcomes	Critical and important outcomes: mortality (all causes), cardiovascular death, death from kidney causes, need for initiation of RRT, doubling of serum creatinine, new onset of albuminuria > 300 mg/g, kidney composite, major adverse cardiovascular events, heart failure, myocardial infarction, stroke, treatment dropouts due to adverse effects, serious adverse effects, hyperkalemia, HbA1c (%), eGFR, % change from baseline uACR, diabetic retinopathy progression, diabetic ketoacidosis, urinary tract infections, gastrointestinal adverse effects, hypoglycemia, amputations, fractures.
Study design	RCT
Guideline Chapter 3	Blood pressure control in people with diabetic kidney disease
Clinical question	In patients with T1D or T2D and CKD, what is the target blood pressure levels?
Population	Adults with CKD (G1–G5, G5D, G1T–G5T) and diabetes (T1D or T2D)
Intervention	Intensive blood pressure control
Comparator	Standard blood pressure control
Outcomes	Critical and important outcomes: systolic and diastolic blood pressure, need for initiation of RRT, doubling of serum creatinine, eGFR, uACR, mortality (all causes), cardiovascular death, heart failure, myocardial infarction, hyperkalemia and treatment dropouts due to adverse effects.
Study design	RCT
Clinical question	In patients with T1D or T2D and CKD, what are the effects of different therapies for hypertension on clinically relevant outcomes and clinically relevant harms?
Population	Adults with CKD (G1–G5, G5D, G1T–G5T) and diabetes (T1D or T2D)
Intervention	Possible therapies: ARBs, ACEi, nonsteroidal MRA, aliskiren
Comparator	Other therapies/standard of care/placebo
Outcomes	Critical and important outcomes: systolic and diastolic blood pressure, need for initiation of RRT, doubling of serum creatinine, eGFR, uACR, mortality (all causes), cardiovascular death, heart failure, myocardial infarction, hyperkalemia and treatment dropouts due to adverse effects.
Study design	RCT
Guideline Chapter 4	Treatment targeting progression of CKD in people with diabetic kidney disease
Clinical question	In patients with T1D or T2D and CKD, what are the effects of different therapies targeting progression of CKD on clinically relevant outcomes and clinically relevant harms?
Population	Adults with CKD (G1–G5, G5D, G1T–G5T) and diabetes (T1D or T2D)
Intervention	Possible therapies: ARBs, ACEi, steroidal and nonsteroidal MRA, aliskiren, SGLT2i, GLP1RA, GLP1 RA/GIP, DPP4i, pentoxifyline, protein restriction
Comparator	Other therapies/standard of care/placebo
Outcomes	Critical and important outcomes: mortality (all causes), cardiovascular death, death from kidney causes, need for initiation of RRT, doubling of serum creatinine, new onset of albuminuria > 300 mg/g, kidney composite, major adverse cardiovascular events, heart failure, myocardial infarction, stroke, treatment dropouts due to adverse effects, serious adverse effects, hyperkalemia, HbA1c (%), eGFR, % change from baseline uACR, diabetic retinopathy progression, diabetic ketoacidosis, urinary tract infections, gastrointestinal adverse effects, hypoglycemia, amputations, fractures.
Study design	RCT

Table 1 – (*continued*)	
Guideline Chapter 5	Antiplatelet or anticoagulant therapy in people with diabetes and CKD
Clinical question	In patients with T1D or T2D and CKD, what are the indications and effects of antiplatelet or anticoagulant therapy on clinically relevant outcomes and clinically relevant harms?
Population	Adults with CKD (G1–G5, G5D, G1T–G5T) and diabetes (T1D or T2D)
Intervention	Antiplatelet (acetylsalicylic acid, phosphodiesterase inhibitors: dipyridamole and cilostazol, and P2Y12 inhibitors: clopidogrel, prasugrel and ticagrelor) and anticoagulant therapy (acenocoumarol, warfarin, apixaban, rivaroxaban, edoxaban and dabigatran)
Comparator	Placebo/other therapy
Outcomes	Critical and important outcomes: mortality (all causes), cardiovascular death, death from kidney causes, myocardial infarction, stroke, treatment dropouts due to adverse effects, serious adverse effects, hemorrhage.
Study design	RCT

ACEi: Angiotensin-converting enzyme (ACE) inhibitors; ARBs: Angiotensin receptor blockers; CKD: Chronic Kidney Disease; DPP-4: dipeptidyl peptidase 4; eGFR: Estimated Glomerular Filtration Rate; G1-G5: grade 1-5, G5D: grade 5 dialysis; G1T-G5T: grade 1-5 transplant; GIP: Gastric inhibitory polypeptide; GLP-1 RA: Glucagon-like peptide-1 receptor agonists; HbA1c: glycated haemoglobin; MRA: mineralocorticoid receptor antagonist; RCT: randomised controlled trial; SGLT2i: Sodium-glucose cotransporter 2 inhibitors; T1D: Type 1 diabetes; T2D: Type 2 diabetes; uACR: Urine Albumin-to-Creatinine Ratio.

comparisons. In this last case, for dichotomous outcomes, both the number of events and the total number of patients were divided up and for continuous outcomes, only the total number of participants were divided up and the means and standard deviations were left unchanged.

Evaluation of important numerical data such as screened, randomized patients, intention-to-treat (ITT), as-treated, and per-protocol (PP) population was carefully performed. Dropouts, losses to follow-up and withdrawals were investigated. Issues of missing data and imputation methods were critically appraised. Heterogeneity was analyzed using a Chi-squared test on $N-1$ degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test. I^2 values of 30–60%, 50–90%, and 75–100% correspond to moderate, substantial and considerable levels of heterogeneity. Funnel plots were used to assess the potential existence of small study bias.

Summary of findings (SoF) tables were developed to include a description of the population and the intervention and comparator. In addition, the SoF tables included results from the data synthesis as relative and absolute effect estimates. The grading of the quality of the evidence for each critical and important outcome is also provided in these tables. The SoF tables are available in Appendix 3 (Suppl. Materials).

7. *Grading the strength of the recommendations based on the quality of the evidence using the GRADE approach*. For rating guideline recommendations, the GRADE (Grading of Recommendations Assessment, Development and Evaluation) nomenclature was used.[5] The strength of individual recommendations was rated as strong (Level 1) or weak (Level 2), and the quality of the supporting evidence was shown as A (high), B (moderate), C (low), or D (very low) (Appendix 4, Suppl. Materials).
8. *Finalizing guideline recommendations and supporting rationale*. The steering committee integrated the literature evidence and wrote the graded recommendations and the underlying rationale, graded the strength of the recommendations and developed practice points.
9. *Convening a public review of the guideline draft in December 2023*.
10. *Amending the guideline based on the external review feedback*. A committee of validating experts validated the recommendations using the AGREE II guidelines.[2]
11. *Finalizing and publishing the guideline*.

Summary of recommendation statements

Chapter 1: Screening and diagnosis of diabetic kidney disease

Recommendation 1.1. Annual screening is recommended for the detection of diabetic kidney disease. In type 1 diabetes (T1D), this should start five years after the diagnosis of diabetes, and in type 2 diabetes (T2D) or Latent Autoimmune Diabetes in Adults (LADA), from the moment the disease is detected. Measurement of the presence of albuminuria (evaluating urine albumin-to-creatinine ratio of a random urine sample) and evaluation of estimated glomerular filtration rate (eGFR) using CKD-EPI formulae would be recommendable.

Strength of recommendation: 2D

Rationale: In adult individuals, most guidelines recommend that the assessment of proteinuria should be performed by determination of the uACR, preferably in the first urine of the morning. The urine protein or albumin concentration should always be referred to as the creatinine concentration to minimize the effect of the degree of hydration (urine concentration). This result approximates to the 24-h loss if there is no large body surface area deviation.[6–9] It must be considered that there is high variability among albuminuria measurements, so to confirm the existence of pathological albuminuria, more than one sample is required.[10,11] Factors that may influence albuminuria determination independent of kidney damage are exercise, infections, fever, congestive heart failure, menstruation and hyperglycemia or very high blood pressure.[12] Two elevated values in three samples obtained at least three months apart are necessary to consider the presence of significant albuminuria. UPCR is recommended in patients with suspected renal interstitial pathology (Sjögren's syndrome, antiretroviral nephrotoxicity, etc.) since in these situations

proteinuria is mainly produced by low molecular weight tubular proteins other than albumin. The existence of a significant dissociation between the uACR and protein-to-creatinine ratio should also suggest the possibility of the presence of free light chains in the urine (Bence–Jones proteinuria) or immunoglobulins (as in impure nephrotic syndrome).

On the other hand, there are various methods that can be used to measure GFR: creatinine clearance measured in 24-hour urine, creatinine clearance estimated by the Cockcroft-Gault formula, glomerular filtration rate estimated by MDRD, EKFC or CKD-EPI equations with creatinine (2009) or the CKD-EPI creatinine-cystatin equation (2021), glomerular filtration rate measured by isotopic methods, or glomerular filtration rate measured by iohexol. At present, the most frequently used method is estimation of eGFR using the CKD-EPI creatinine equation, which is implemented in practically all hospital and health center laboratories.[13,14] Cystatin C-based methods have the disadvantage of being expensive and not commonly implemented in laboratories, but are likely more reliable, especially in older populations or patients with illness other than CKD (heart failure, cancer, malnutrition, cirrhosis) and its measurement is advocated by some guidelines. Isotopic methods are very reliable but can only be applied in a hospital setting.[15,16] It is very probable that in the near future, we will see a more common use of GFR measurement by iohexol, which seems very reliable but is not yet widespread.[17]

There are other methods that can be used to evaluate kidney disease in patients with diabetes: (a) Reno-vesical ultrasound: some studies suggest ultrasonographic data that may give rise to suspicion of the presence of nephropathy as well as to make a differential diagnosis with other causes[18,19] or (b) other biomarkers in the early detection of kidney disease in patients with diabetes,[20–28] such as inflammation, endothelial dysfunction and urinary and tubular markers, GWAS genetic studies and others (cystatin, NAG, NGAL, KIM-1, IL-6, Netrin-1, thrombospondin-2, urinary glycans, urinary exosomes, VEGF, galectin-3, GDF-15, soluble TNF alpha). At present, several research groups are working on biomarker batteries or combined systems with multiple data (gradient boosting machines), which for now are difficult to apply in daily clinical practice.[29–37] Therefore, we believe that more evidence needs to be generated. We recommend the application of well-recognized biomarkers, even if they can be surrogated.

Recommendation 1.2. Referring people with diabetes to a nephrologist may be appropriate in any situation where a physician needs assistance in managing diabetic kidney disease according to current recommendations.

Strength of recommendation: 2D

Rationale: The situations where evaluation by a nephrologist would be recommendable are:

1. Albuminuria of uACR > 300 mg/g maintained in two successive controls.[9]
2. Reduced eGFR: To date, all consensus documents and Clinical Practice Guidelines recommend referral of patients with diabetes when eGFR < 30 ml/min/1.73 m^2 or when there is uACR > 300 mg/g. However, recent publications suggest earlier referral, for shared control with primary care physicians and other specialists involved in the care of patients with T1D and T2D[38] and as a more appropriate practice for better early "prevention" of diabetic kidney disease.
3. Rapid decline of kidney function: A patient can be considered to have renal progression when there is a decrease in eGFR > 5 ml/min/year or >10 ml/min in five years. Progression is defined based on two aspects: progression to a higher or more severe category of kidney function impairment (KDIGO stages 1–5) or albuminuria (<30, 30–299, >300 mg/g). Progression is also considered as a percentage change from baseline (>25% deterioration in eGFR) or more than a 50% increase in the uACR ratio. However, it should be noted that a recent international consensus document to define renal progression outcomes indicates decreases of 30, 40, 50 or 57% of kidney function as possible surrogates for "progression", depending on factors such as the rate of progression, the choice of initial eGFR starting point or the effect of interventions with acute consequences on eGFR.[39]
4. Poorly controlled arterial blood pressure: systolic blood pressure (SBP) > 140 mm Hg and/or diastolic blood pressure (DBP) > 85 mm Hg despite adequate antihypertensive treatment or resistant arterial hypertension (BP ≥ 180/110 mm Hg despite treatment with three antihypertensive drugs at maximum tolerated dose, one of which is a diuretic).
5. Renal anemia with hemoglobin (Hb) of <10 g/dL requiring treatment with erythropoiesis-stimulating agents after having excluded other causes (iron, folate or cobalamin deficiency).[40]
6. Disorders of acid–base balance: primarily uncontrolled metabolic acidosis.
7. Deterioration of kidney function after initiation of renin–angiotensin–aldosterone system (RAAS) inhibitors or iSGLT2: decrease in eGFR, maintained and not reversible equal to or greater than 30% over baseline or hyperkalemia greater than 5.5 mEq/L, not controllable.[41]
8. Doubts about whether there is nondiabetic renal involvement: Potential differential diagnoses will be raised and should be referred to the nephrologist for evaluation, in case of: active urinary sediment (presence of hematuria); absence of diabetic retinopathy; short duration of diabetes over time or well-controlled HbA1c; associated systemic symptomatology that raises suspicion of other pathologies; rapid progression of kidney dysfunction or rapid increase in proteinuria or the presence of nephrotic syndrome.

Recommendation 1.3. Performing a kidney biopsy on people with diabetes should be indicated in the following situations: (1) when there is a rapid increase in proteinuria or nephrotic range proteinuria, (2) proteinuria > 1 g/day in 24 h urine collection in diabetes with under five years of progress, (3) deterioration of kidney function with and without diabetic retinopathy, (4) alterations in the urinary sediment (dysmorphic red blood cells) not associated with an infectious process (urinary infection), (5) rapid decrease in eGFR in patients with previous stable kidney function or (6) clinical and/or analytical signs of associated immune disease.[42,43]

Strength of recommendation: 2D

Rationale: Some studies have described the following factors associated with nondiabetic kidney lesions: elevated SBP,

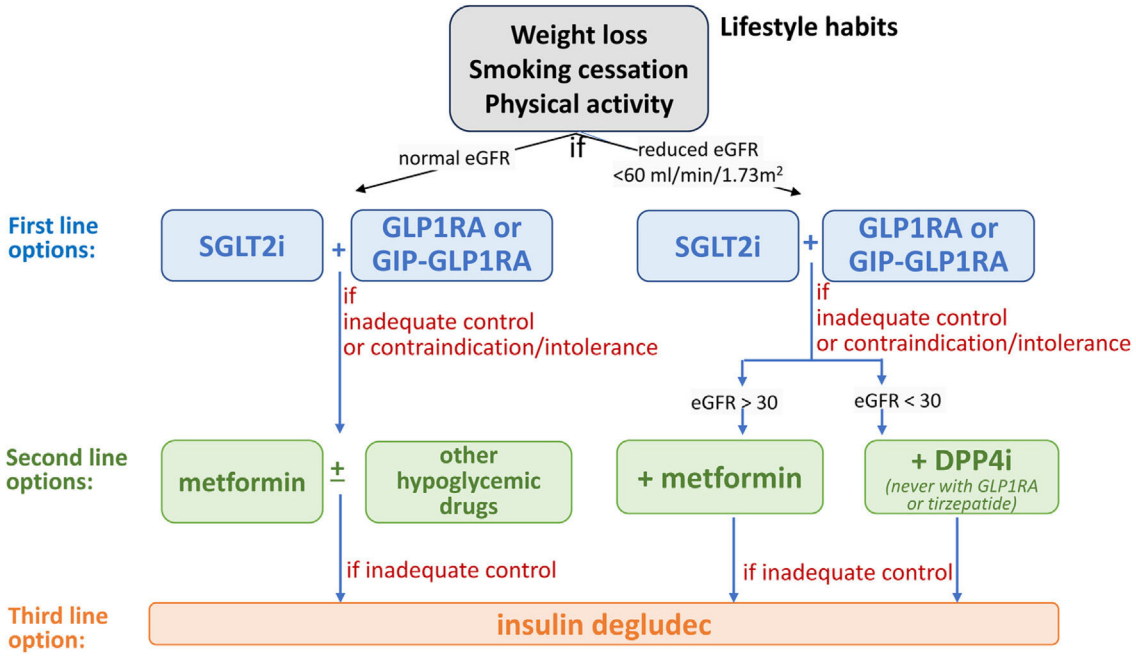

Fig. 1 – Drug therapy for metabolic control in patients with T2D and CKD.

adequate HbA1c, short duration of diabetes, and absence of retinopathy.[44] Diabetic retinopathy has high sensitivity (87%) and specificity (93%) in predicting more severe histological lesions of diabetic kidney disease. However not all studies show the same results, as some often describe histologic lesions of diabetic kidney disease in the absence of diabetic retinopathy.[45]

The presence of a nondiabetic kidney disease can lead to different treatments depending on the underlying pathology and, therefore, to a different prognosis. Progression to advanced CKD is much higher in patients with diabetic kidney disease (44%), compared to mixed forms (18%) or nondiabetic forms (12%). Fiorentino et al.[46] published a meta-analysis including 48 studies of kidney biopsies in patients with diabetes, including a total of 4876 biopsies. It showed a highly variable prevalence of diabetic nephropathy (6.5–94%), nondiabetic nephropathies (3–83%) and mixed forms (4–45%). Their first important conclusion is that the diagnosis of nondiabetic nephropathy is very high, with IgA nephropathy being the most frequent (3–59%).

It is important to consider the potential risks and benefits of performing a kidney biopsy for each individual patient before indicating it.

Chapter 2: Metabolic control in people with diabetes and CKD

As primary prevention, strict metabolic control is the most effective intervention to achieve nephroprotection, both in T1D and T2D.[47] The lower the HbA1c value obtained, the lower the risk of albuminuria, as strict metabolic control decreases the risk of the onset and progression of CKD in people with diabetes. In T2D, better glycemic control is also associated with fewer microangiopathic complications and reduced progression of albuminuria: in secondary prevention, tight glycemic control may decrease the progression of albuminuria. HbA1c < 7% is recommended on an individualized basis and targets of lower than 6.5% could be considered in patients with a long life expectancy, provided that they can be achieved with glucose-lowering drugs with no risk of hypoglycemia. Similarly, less stringent targets (<8%) are valid in patients with a history of severe hypoglycemia, short life expectancy, or extensive microvascular or macrovascular complications that require treatment with insulin, glinides or sulphonylureas. Nonetheless, the HbA1c target should be adapted to the possible risk of hypoglycemia of the antihyperglycemic drugs prescribed. The use of continuous glucose monitoring hypoglycemia could potentially prevent hypoglycemia.

Lifestyle interventions must be an important part of care for people with diabetes and CKD and should be reinforced, as low sodium intake, physical exercise and smoking cessation are cornerstones of treatment. In any case, most patients will need dietary advice and selected drugs for a comprehensive approach to the disease.

Recommendation 2.1. Patients with T2D and CKD should be treated with a sodium-glucose cotransporter-2 inhibitor (SGLT2i) and, if necessary, additional pharmacological treatment required to improve glycemic control (Table S2.1).

Strength of recommendation: 1B

Rationale: In recent years, the emergence of SGLT2i has represented a major leap forward in the evidence base for cardiorenal protection in CKD. SGLT2i should be used as the first line of therapy for most of the population considering the eGFR (Fig. 1), as SGLT2i have proven to decrease CKD onset, progression, and major adverse cardiovascular events (MACE) in patients with T2D, irrespective of their effect on glycemic control.

Table 2 – Studies with SGLT2i in patients with T2D and CKD.

Trials	Year of completion	SGLT2i	Patient population	Number of patients; median follow up	HbA1C (% reduction)	CV outcome			Kidney outcome		
							SGLT2i vs. placebo group	HR (95%CI)		SGLT2i vs. placebo group	HR (95%CI)
EMPA REG[83]	2015	Empagliflozin (10/25 mg)	T2D and CV disease	7020 3.1 years	0.24% (95% CI, 0.40 to 0.08)	MACE	10.5 vs. 12.1%	0.86 (0.74–0.99)	(Post hoc) Incident or worsening nephropathy or CV death	16.2 vs. 23.6%	0.61 (0.55–0.69)
						HF or CV death (excluding fatal stroke)	5.7 vs. 8.5%	0.66 (0.55–0.79)	Incident or worsening nephropathy	12.7 vs. 18.8%	0.61 (0.53–0.7)
						CV death	3.7 vs. 5.9	0.62 (0.49–0.77)	Doubling of serum creatinine	1.5 vs. 2.6%	0.56 (0.39–0.79)
									Initiation of kidney replacement therapy	0.3 vs. 0.6%	0.45 (0.21–0.97)
CANVAS[148]	2017	Canagliflozin (100, 300 mg)	T2D and high CV disease risk	10,142 2.6 years		MACE	26.9 vs. 31.5%	0.86 (0.75 –0.97)	Progression of albuminuria	89.4 vs. 128.7 per 1000 patient years	0.73 (0.67–0.79)
						Hospitalization for HF	5.5 vs. 8.68 per 1000 patients/year	0.67 (0.52–0.87)	Sustained 40% reduction in eGFR, need for kidney replacement therapy, or death from kidney causes	5.5 vs. 9.0	0.60 (0.47–0.77)
DECLARE-TIMI58[84]	2018	Dapagliflozin (10 mg)	T2D and ≥1 CV disease risk factor	17,160 4.6 years	0.42%; 95% confidence interval [CI], 0.40–0.45).	MACE	8.8 vs. 9.4%	0.93 (0.84–1.03)	≥40% reduction in eGFR, ESKD ≥90 days, (dialysis, sustained eGFR < 15 ml/min/1.73 m^2, or kidney transplantation), or renal/CV death	4.3 vs. 5.6%	0.76 (0.67 –0.87).
						CV death or hospitalization for HF	4.9 vs. 5.8%	0.83 (0.73 –0.95)			
CREDENCE[48]	2019	Canagliflozin (100 mg)	T2DM and CKD	4401		MACE	9.9 vs. 12.2%	0.80 (0.67–0.95)	Doubling of serum creatinine, ESKD (dialysis, kidney transplantation, or sustained eGFR < 15 ml/min/1.73 m^2), or renal/CV death	11.1 vs. 15.4%	0.70 (0.59–0.82)
						HF or CV death	8.1 vs. 11.5%	0.69 (0.57–0.83)			

Table 2 – (*continued*)

Trials	Year of completion	SGLT2i	Patient population	Number of patients; median follow up	HbA1C (% reduction)	CV outcome			Kidney outcome		
							SGLT2i vs. placebo group	HR (95%CI)		SGLT2i vs. placebo group	HR (95%CI)
DAPA-CKD[49]	2020	Dapagliflozin (5/10 mg)	CKD (T2D and nondiabetics)	4304 2.4 years	–0.9 [95% CI –1.5, 0.3])	Death CV causes or hospitalization for HF	4.6 vs. 6.4%	0.71 (0.55–0.92)	Decline in e-GFR of at least 50%, ESKD, or death from kidney or CV causes	9.2 vs. 14.5%	0.61 (0.51 –0.72)
									Sustained decline in the eGFR of at least 50%, ESKD, or death from kidney causes	6.6 vs. 11.3%	0.56 (0.45 – 0.68)
EMPA-kidney[50]	2022 Early stop due to evidence of efficiency	Empagliflozin (10 mg)	CKD (T2D and nondiabetics)	6609	44.52 mml/mmol (0.14) vs. 44.90 mmol/mmol (0.14) Absolute difference −0.39 (−0.77, −0.01)	Hospitalization for HF or cardiovascular death	4 vs. 4.6%	0.84 (0.67–1.07)	ESKD, a sustained decline in eGFR to <10 ml/min/1.73 m^2, renal death, or a sustained decline of ≥40% in eGFR from randomization or Cardiovascular death	4.9 vs. 6.6%	0.73 (0.59–0.89)
						Occurrences of hospitalizations from any cause	No. of events/100 patient-year 24.8 vs. 29.2	0.86 (0.78–0.95)			
						Death from any cause	4.5 vs. 5.1%	0.87 (0.70–1.08)			

CI: Confidence Interval; CKD: chronic kidney disease; CV: cardiovascular; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; HbA1c: glycated haemoglobin; HF: heart failure; HR: Hazard Ratio; MACE: major adverse cardiovascular events; T2D: type 2 diabetes; SGLT2i: Sodium-glucose cotransporter 2 inhibitors.

SGLT2i decrease hyperglycemia by increasing urinary glucose excretion, since the SGLT2 cotransporter is responsible for 90% of glucose reabsorption in the proximal tubule. SGLT2i were first found to have cardiovascular and kidney-protective effects in cardiovascular safety trials, in which nephroprotection was a secondary endpoint. In April 2019, the CREDENCE study[48] was published. It was the first clinical trial to investigate the effects of SGLT2i on patients with DM and CKD (eGFR ≥ 30 ml/min/1.73 m^2 and albuminuria ≥ 300 mg/g) with primary kidney targets. Canagliflozin decreased the incidence of kidney events (advanced CKD, doubling of serum creatinine, or renal or cardiovascular death) by 30%. The magnitude of the benefit caused the trial to stop prematurely. The DAPA-CKD trial[49] (Dapagliflozin and Prevention of Adverse Outcomes in CKD) enrolled participants with and without T2D, demonstrating cardiorenal benefits in both groups. EMPA-KIDNEY (The Study of Heart and Kidney Protection With Empagliflozin)[50] studied the effect of another SGLT2i, empagliflozin, and demonstrated similar results in a wider CKD population, thus confirming the benefit of SGLT2 inhibition on the risk of progression of kidney disease or death from cardiovascular causes in diabetic and nondiabetic CKD in a wider spectrum of patients. This study included patients without albuminuria, previously underrepresented in most of the trials. It showed that SGLT2i agents have evidence-based benefits in reducing the rate of progression of CKD to kidney failure. In summary, SGLT2i should be prescribed to eligible patients to address the global burden of diabetic kidney disease, CKD and its cardiovascular complications independently of glycemic control, as the improvement in HbA1c is quite modest in patients with low eGFR (Table 2).

This guideline recommends the use of SGLT2i as nephroprotective agents in patients with T2D and an eGFR > 20 ml/min/1.73 m^2, independently of the use of metformin. SGLT2i should be continued until end-stage kidney disease (dialysis or kidney transplant). Given their mechanism of action, kidney and cardiovascular protective effects persist even when the GFR decreases < 45 ml/min/1.73 m^2 where the effect on lowering glycemia is minimal.

Recommendation 2.2. Glucagon-like peptide-1 receptor agonists are recommended as additional pharmacological treatment, as they have proven cardiovascular benefit and, recently, kidney benefit in terms of CKD progression in people with T2D (Tables S2.2–S2.10).

Strength of recommendation: 1B

Rationale: GLP1RA provide cardiovascular protection in patients with CKD. Moreover, both SGLT2i and GLP1RA have proven cardio-kidney-metabolic benefits both in patients with or without metformin[51] (GLP1RA (mainly semaglutide) have proven CV and kidney benefits. In addition, they are safe in patients with CKD, even with an eGFR as low as 15 ml/min/1.73 mm^2.

Current GLP1RA are GLP-1 analogs, which are gut-derived incretin hormones that promote insulin secretion by stimulating GLP1 receptors and decrease glucagon secretion after a meal by stimulating pancreatic GLP1 receptors. They induce weight loss, increase satiety sensation and initially slow gastric emptying. GLP1ra have also proven to lower blood pressure and albuminuria in RCT. Preclinical studies suggest that GLP-1RA regulate kidney inflammation. GLP-1RA inhibited AGE-stimulated IL-6 and TNF-α production in mesangial cells and diabetic rats treated with GLP-1RA showed inhibition of renal NF-κB activation, decreasing proinflammatory factors (TNF-α, IL-1β and CCL-2) and reduced oxidative stress. Information on GLP1ra anti-inflammatory actions in CKD is limited. In this regard, REMODEL[52] will evaluate anti-inflammatory mechanisms of kidney protection by semaglutide.[53]

Cardiovascular safety trials such as REWIND (dulaglutide),[54] LEADER (dulaglutide),[55] SUSTAIN6 (semaglutide),[56] HARMONY (albiglutide)[57] and AMPLITUDE (efpeglenatide)[58] demonstrated a reduction in risk of CVD events, even in patients with decreased kidney function. In major kidney secondary outcomes, these trials have shown a decrease in albuminuria and lower glomerular filtration loss, mostly by decreasing albuminuria in populations with T2D and CKD. However, changes in glucose control, weight or blood pressure only account for 10–25% of kidney benefits, suggesting that these drugs have additional effects on kidney protection. In this regard, ongoing RCT are trying to address the mechanisms for kidney protection in diabetic kidney disease[52] with subcutaneous semaglutide (Table 3).

The FLOW study (Evaluate Renal Function with Semaglutide Once Weekly)[59] is the first GLP1RA clinical trial with a kidney endpoint as a primary outcome using subcutaneous semaglutide at a dose of 1 mg once weekly. It evaluated the effect of semaglutide in 3533 participants with T2D, eGFR 25–75 ml/min/1.73 m^2 and albuminuria 100–5000 mg/g. It prematurely stopped after the interim analysis demonstrated efficacy. In terms of metabolic control, semaglutide had an increased effect on lowering HbA1c (−0.87% vs. −0.06%, estimated difference −0.81 (95%CI −0.9 to 0.72%).

Tirzepatide is a dual agonist of the glucose-dependent insulinotropic polypeptide (GIP) and GLP1 receptors (twincretin). Tirzepatide is currently the most effective drug in glycemic control and weight loss in patients with type 2 diabetes, showing superiority in clinical trials over semaglutide 1 mg or basal insulins and without risk of hypoglycemia. Despite this evidence, the drug has not yet received FDA (Food and Drug Administration) approval. It also improves other cardiorenal risk factors (blood pressure, LDL cholesterol and albuminuria) in populations with type 2 diabetes or obesity. The SURPASS-4 trial[60] studied the effect of tirzepatide on participants with T2D and high cardiovascular risk. It improved a prespecified secondary composite kidney endpoint (eGFR decline ≥40% from baseline, renal death, kidney failure, or new onset albuminuria > 300 mg/g) when compared to insulin glargine, although the risk reduction was mainly driven by albuminuria of >300 mg/g reduction. Tirzepatide also slowed a decline of eGFR, but to our knowledge, there are no RCTs evaluating this drug in a trial with kidney endpoints as primary outcomes so far.

DPP-4 inhibitors modestly lower blood glucose with a low risk of hypoglycemia and can be used in fragile patients or those with intolerance or contraindications to GLP-1RAs, but have not demonstrated an improvement in kidney or cardiovascular outcomes. They must not be used in combination with GLP1RA.

Table 3 – Randomized clinical trials with GLP1RA in patients with T2D and CKD.

	N	Drug	Dose	HbA1c decrease	MACE-3	Composite kidney outcome including albuminuria > 300 mg/g	Worsening of kidney function
ELIXA[149]	6068	Lixisenatide	20 μg per day	0.27 (0.31–0.22)	1.02 (0.89–1.17)	0.84 (0.68–1.02)	1.16 (0.74–1.83)
LEADER[150]	9340	Liraglutide	1.8 mg per day	0.40 (0.45–0.34)	0.87 (0.78–0.97)	0–78 (0.67–0.92)	0.89 (0.67–1.19)
SUSTAIN-6[56]	3297	Semaglutide sc	1 mg per week	1.1 (1.2–0.9)	0.74 (0.58–0.95)	0.64 (0.46–0.88)	1.28 (0.64–2.58)
EXSCEL[151]	14,752	Exenatide	2 mg per week	0.53 (0.57–0.50)	0.91 (0.83–1.00)	0.88 (0.76–1.01)	0.88 (0.74–1.05)
HARMONY OUTCOMES[57]	9463	Albiglutide	30 or 50 mg per week	0.52 (0.58–0.45)	0.78 (0.68–0.90)	-	-
REWIND[152]	9901	Dulaglutide	1.5 mg per week	0.61 (0.58–0.65)	0.88 (0.79–0.99)	0.85 (0.77–0.93)	0.70 (0.57–0.85)
PIONEER 6[93]	3183	Semaglutide oral	14 mg per day	1 (1.2–0.9)	0.79 (0.57–1.11)	-	-
FLOW[59]	3533	Semaglutide sc	1 mg per week	0.81 (0.9–0.72)	0.82 (0.68–0.98)	0.79 (0.66–0.94)	0.73 (0.59–0.89)

Metformin must not be used in patients with eGFR below 30 ml/min/1.73 m^2 due to the risk of secondary lactic acidosis and must be used cautiously in patients with eGFR between 30 and 44 ml/min/1.73 m^2, reducing the drug to a maximum of 1000 mg/day. DPP-4 inhibitors, GLP-1RAs and SGLT2i can be prescribed in patients with advanced CKD. The antihyperglycemic effect of the first two classes is maintained in this population and although this effect is partially lost with SGLT-2i, they are also recommended for their CV and kidney benefit.

Treatment with sulfonylureas or glinides is not recommended in patients with lower GFR as they can induce hypoglycemia.

Insulin and high doses of glitazone should be avoided, where possible, in people with CKD and T2DM, as this decreases natriuresis and increases fluid retention.[61] If treatment with insulin is required, the dose should be adjusted and lowered in the event of CKD progression because of its delayed renal elimination.[61,62] If the patient requires insulin, basal insulin therapy with insulin analogs is recommended, due to the lower risk of hypoglycemia. In a CV safety trial (DEVOTE), insulin degludec showed a lower risk of severe hypoglycemia versus glargine U100 in patients with DM2 and high CV risk (including patients with CKD).[55]

In light of new evidence and results in kidney and cardiovascular protection, recommendations cannot only be made on glycemic control and would go beyond metabolic intervention, since new therapeutic groups act on several aspects.

Table 4 and Fig. 1 summarize the key points about the treatment of people with diabetes and chronic kidney disease.

Chapter 3: Blood pressure control in people with diabetic kidney disease

Recommendation 3.1. We recommend blood pressure (BP) control with a target systolic blood pressure (SBP) of <130 mm Hg, when tolerated, in patients with diabetic kidney disease. Otherwise, a general target of SBP < 140 mm Hg is recommended (Table S3.1).

Strength of recommendation: 2C

Rationale: There is evidence from the SPRINT trial that intensive blood pressure control, defined as targeting systolic blood pressure < 120 mm Hg, reduces cardiovascular events and all-cause mortality in CKD patients.[63] However, the SPRINT trial exclusively involved participants who did not have diabetes and the benefits observed in the SPRINT trial are not evident in studies involving patients with diabetes. Specific evidence on the blood pressure control target in patients with chronic kidney disease and diabetes is very limited, and the evidence is generated from clinical trials that include patients with diabetes mellitus, both with and without kidney disease.

Upon reviewing the ACCORD BP,[57] ADVANCE[58] and ABCD[59] trials, which involved patients with diabetes with and without CKD, intensive control of blood pressure might lead to minimal or no variation in all-cause and cardiovascular mortality compared to standard blood pressure control.[55,63,64] Some studies examined cardiovascular events,[64,65] and intensive blood pressure control may not be associated with better outcomes. When cardiovascular events were evaluated separately, intensive blood pressure control in patients with CKD and diabetes may result in little to no difference in stroke[65–67] and heart failure.[65–67] However, such control might reduce the risk of myocardial infarction,[57–59] although the quality of evidence is moderate. The ACCORD BP trial did demonstrate a significant reduction in stroke in the intensive blood pressure control group.

Therefore,[55,63,64] to generate recommendations for CKD and T2D, certain trial characteristics must be taken into consideration. We must consider that most of the patients included in these trials presented albuminuria as a manifestation of kidney disease. In most of them, the mean creatinine levels were normal and with well-preserved eGFR.[64–66] In the ACCORD BP trial, only patients with T2D were included, and individuals with a serum creatinine level greater than 1.5 mg/dL (132.6 μmol/L) were excluded. In the ADVANCE trial, patients might present albuminuria, although this was not mandatory, and the mean serum creatinine was 87 μmol/L in both groups. The ABCD trial included normotensive patients with diabetes without hypertension treatment and the mean

Table 4 – Key points summarizing treatment for metabolic control in patients with T2D and CKD.

1. SGLT-2i are antihyperglycemic drugs with proven cardiovascular and kidney protective effects in patients with T2D, CKD and CHF.
2. GLP1RA are antihyperglycemic drugs that have also shown kidney benefit in patients with CKD and T2D.
3. The rest of the pharmacologic classes (including metformin) have not conclusively shown a reduction in kidney events in patients with T2D.
4. The recommended SGLT2i and GLP1RA are those that have demonstrated reduction of kidney events in clinical trials in T2D designed with this objective (canagliflozin, dapagliflozin, empagliflozin and semaglutide).
5. SGLT2i have a weak antihyperglycemic effect with reduced eGFR, so their combination with other therapeutic classes (preferably with GLP-1RA) is recommended in patients with CKD G3A onwards.
6. GLP-1RA maintains its antihyperglycemic efficacy in patients with advanced CKD.
7. If patients do not have adequate glycemic control with the SGLT2i/GLP1RA combination (or either contraindication or intolerance to any of them), metformin will be prescribed, as long as GFR > 30. DPP4i are an alternative with a weak antihyperglycemic effect in patients with contraindications or intolerance to GLP-1RA.
8. Tirzepatide, a dual GLP-1/GIP agonist, is the drug that has demonstrated the greatest antihyperglycemic efficacy in patients with T2D so far and may be an alternative to GLP-1RA in patients with CKD to improve glycemic control, although there are still no studies published with kidney endpoints and this drug has not yet been approved by the FDA.
9. GLP1RA, DPP4i and tirzepatide do not have an additive or synergistic effect, so they should not be prescribed simultaneously.
10. If patients require insulin, basal insulin therapy with insulin analogs is recommended, due to the lower risk of hypoglycemia. In a CV safety trial (DEVOTE), insulin degludec showed a lower risk of severe hypoglycemia versus glargine U100 in patients with DM2 and high CV risk (including patients with CKD).

CHF: Congestive heart failure; CKD: Chronic Kidney Disease; CV: cardiovascular; DPP4i: dipeptidyl peptidase 4 inhibitors; eGFR: Estimated Glomerular Filtration Rate; FDA: Food and Drug Administration; G3: grade 3; GIP: Gastric inhibitory polypeptide; GLP-1RA: Glucagon-like peptide-1 receptor agonists; SGLT2i: Sodium-glucose cotransporter 2 inhibitors; T2D: Type 2 diabetes.

creatinine clearance was >80 ml/min in both groups. Concerning kidney disease, patients were excluded if they were receiving dialysis and/or had a serum creatinine level greater than 3 mg/dL. In Estacio et al.[64] 129 patients with type 2 diabetes and BP ranging from 140/80 to 90 mm Hg without significant albuminuria were randomized to intensive BP management (diastolic BP target of 75 mm Hg) using valsartan, and moderate BP management (diastolic BP between 80 and 90 mm Hg), initially with a placebo.

In patients with chronic kidney disease (CKD) and diabetes, blood pressure management is particularly crucial due to the compound risk of cardiovascular disease and the progression of kidney impairment. Historically, information about blood pressure targets in these populations was provided by a narrower range of clinical studies that may not fully encapsulate the complexity of patient profiles seen today, such as the increased prevalence of obesity and metabolic syndrome. The introduction of new pharmacotherapeutic agents, including SGLT2 inhibitors, GLP-1 receptor agonists and mineralocorticoid receptor antagonists, has significantly broadened treatment options. These agents offer benefits beyond blood pressure reduction, including improved cardiovascular outcomes and slowed CKD progression.

The evolving patient demographics and the availability of these novel therapeutic options highlight the need for contemporary clinical trials. These trials should investigate blood pressure targets tailored to the nuanced needs of CKD and diabetic patients, taking into account the wider spectrum of comorbidities and the potential for improved outcomes with new treatments.

Recommendation 3.2. We recommend starting ACEI or ARB for patients with either hypertension or diabetic kidney disease (Tables S3.2, S3.3).

Strength of recommendation: 2B

Recommendation 3.3. Steroidal MRA are probably useful for managing hypertension in patients with eGFR > 30 ml/min/1.73 m^2 and serum potassium < 4.8 mmol/L (Table S3.4).

Strength of recommendation: 2D

Recommendation 3.4. Although nonsteroidal MRA may be helpful in blood pressure control, we do not recommend them for blood pressure management (Table S3.5).

Strength of recommendation: 2B

Rationale: The different effects of angiotensin II receptor antagonists (ARBs) on blood pressure control compared to angiotensin-converting enzyme inhibitors (ACE inhibitors) are not well-defined.[66,67]

Only two RCTs with a low number of participants evaluated this outcome and the authors showed a trend toward better BP control in patients treated with ARBs compared to ACEI.[67–71]

In terms of BP control, ARBs can reduce systolic BP, but may produce a slight reduction or no difference in diastolic BP compared to the standard treatment.[72–74] In the RENAAL,[72] the ORIENT[73] and the Irbesartan Diabetic Trial,[74] the primary outcome was the kidney outcome, a composite of doubling of the baseline serum creatinine, the onset of end-stage kidney disease, a need for chronic dialysis and/or transplantation and all-cause death. Based on these three RCTs,[72–74] ARBs may be beneficial in terms of kidney outcomes compared to standard blood pressure control, despite similar BP control between the groups.

In terms of cardiovascular outcomes, ARBs probably reduce the risk of heart failure and myocardial infarction compared to placebo or standard of care,[72,73] but ARBs did not reduce the risk of all-cause mortality.[72–74]

Even though the quality of evidence is low due to the serious risk of inconsistency and imprecision, ARB may result in a

slightly higher risk of no difference in hyperkalemia compared to standard of care.[73,74]

Moreover, evidence regarding the use of steroidal MRA in patients with diabetes and proteinuria is very limited, as only a few small-scale studies[75,76] have analyzed this. Based on 86 patients and with low quality of evidence due to the serious risk of bias and imprecision, steroidal MRA may reduce both SBP and DBP, and may reduce uACR compared to standard of care.[74–76]

As blood pressure reduction related to nonsteroidal MRA was modest using finerenone in the FIDELIO-DKD study[77] or esaxerenone,[78] it was hypothesized that the beneficial effect on cardiorenal outcomes was primarily influenced through non-hemodynamic pathways. The ARTS-DN trial[79] was designed to deepen the effect of finerenone on albuminuria and assessed the effects of the treatment on 24-hour ambulatory BP monitoring in a subset of 240 participants. In this group of patients, 24-h ambulatory BP monitoring was measured at baseline, 60 days after the start of finerenone and at the last on-treatment visit. These trials suggest that nonsteroidal MRA may reduce SBP and slightly reduce DBP compared to standard of care.[76,77]

Regarding adverse events, nonsteroidal MRA probably increases the risk of treatment discontinuation due to side effects, with a moderate quality of evidence (RR 1.25 (1.03–1.52)).[77,78] Adding these drugs to a patient already on ACEi/ARB increases the risk of hyperkalemia,[77,78] highlighting the importance of regularly monitoring serum potassium levels in these patients.

Recommendation 3.5. The combination of ACEi with ARB or aliskiren therapy in patients with diabetes and CKD should be avoided (Tables S3.6, S3.7 and S4.4).

Strength of recommendation: 2D

Rationale: The published evidence regarding the use of aliskiren as an antihypertensive therapy in patients with diabetes and chronic kidney disease is very limited. Two[80,81] out of the three studies analyzed compare the use of this drug with ARB, while in the third study, patients received either aliskiren or ARB.[82] Aliskiren may slightly reduce systolic and diastolic blood pressure compared to standard of care, however the evidence is very uncertain.

Chapter 4: Treatment targeting progression of CKD in people with diabetic kidney disease

Recommendation 4.1. Patients with T2D and CKD with an eGFR ≥20 ml/min/1.73 m^2 should be treated with a sodium-glucose cotransporter-2 inhibitor and continue until end-stage kidney disease (dialysis or kidney transplant) (Table S4.7) (Fig. 2).

Strength of recommendation: 1A

Rationale: Patients with T2D and CKD are at increased risk of progression to kidney failure. Currently, there is consistent evidence to confirm that SGLT2i confers significant kidney protective effects in these patients.

The potential for SGLT2i to modify the risk of CKD progression was first demonstrated by a sub-analysis of the EMPA-REG OUTCOME trial in T2D patients with established cardiovascular disease.[83] Analyses plotting mean eGFR against time showed a reduction in the rate of eGFR decline over time, which resulted in a 46% reduction in the risk of the composite kidney disease progression outcome (ESKD, renal death, and doubling of serum creatinine). Benefit is also seen with canaglifozin[48] or dapaglifozin,[84] but not with ertuglifozin.[85]

Three subsequent dedicated clinical trials were designed to test the effect of SGLT2i on CKD progression: CREDENCE,[48] DAPA-CKD[49] and EMPA-KIDNEY.[50] The results from these studies have definitively confirmed the kidney-protective benefits of SGLT2i in patients with T2D and CKD and in a substudy of DAPA-CKD,[86] those who continued with treatment after initiating dialysis had lower mortality levels compared to those who discontinued with it. CREDENCE recruited patients with T2D, an eGFR 30–90 ml/min/1.73 m^2 and a uACR of 300–5000 mg/g under treatment with an ACEi or ARB. Canagliflozin reduced the risk of its primary composite outcome (sustained doubling of serum creatinine, ESKD, or death from kidney or cardiovascular causes) by 30% compared to placebo (HR = 0.70; 95%CI: 0.59–0.82). Importantly, there was a reduction in the risk of kidney disease progression, including ESKD. The risk of maintenance dialysis, kidney transplantation or renal death was significantly reduced by 28%. DAPA-CKD included people with and without T2D. Kidney-related inclusion criteria were an eGFR 25–75 ml/min/1.73 m^2 plus a uACR 200–5000 mg/g and treatment with a stable dose of an ACEi or ARB for ≥4 weeks. Dapagliflozin demonstrated a reduction in the primary composite outcome (sustained 50% decline in eGFR, ESKD, or death from kidney or cardiovascular causes) by 39% compared to placebo (HR = 0.61; 95%CI: 0.51–0.72). It must be noted that these relative risk reductions were again evident for the kidney disease progression component of the primary composite. EMPA-KIDNEY recruited a wide range of participants (with and without T2D) at risk of CKD progression using an eGFR 20–45 ml/min/1.73m^2 (with no indication regarding uACR) or an eGFR ≥45 to <90 ml/min/1.73 m^2 plus a uACR ≥200 mg/g (or protein-to-creatinine ratio ≥300 mg/g) as inclusion criteria. EMPA-KIDNEY reported a reduction in the primary composite outcome of kidney disease progression (sustained decrease in eGFR to <10 ml/min/1.73 m^2, a sustained decrease in eGFR of ≥40% from baseline, ESKD or death from kidney causes) or death from cardiovascular causes, by 28% (HR = 0.72; 95%CI: 0.64–0.82). Similar effects were also observed for the individual components of kidney disease progression.

A unified definition of kidney disease progression was adopted in a comprehensive meta-analysis of large randomized clinical trials with SGLT2i as a sustained eGFR reduction ≥50% from randomization, kidney failure, or death from kidney failure.[87] The results demonstrated an overall 37% reduction in risk of kidney disease progression (HR = 0.63, 95%CI 0.58–0.69), which was similar among participants with and without T2D. In subjects with diabetes, the HR for kidney disease progression outcome was 0.64 (95%CI: 0.52–0.79) in CREDENCE, 0.57 (95%CI: 0.45–0.73) in DAPA-CKD and 0.55 (95%CI: 0.44–0.71) in EMPA-KIDNEY.

Recommendation 4.2. We recommend that treatment with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) should be initiated in

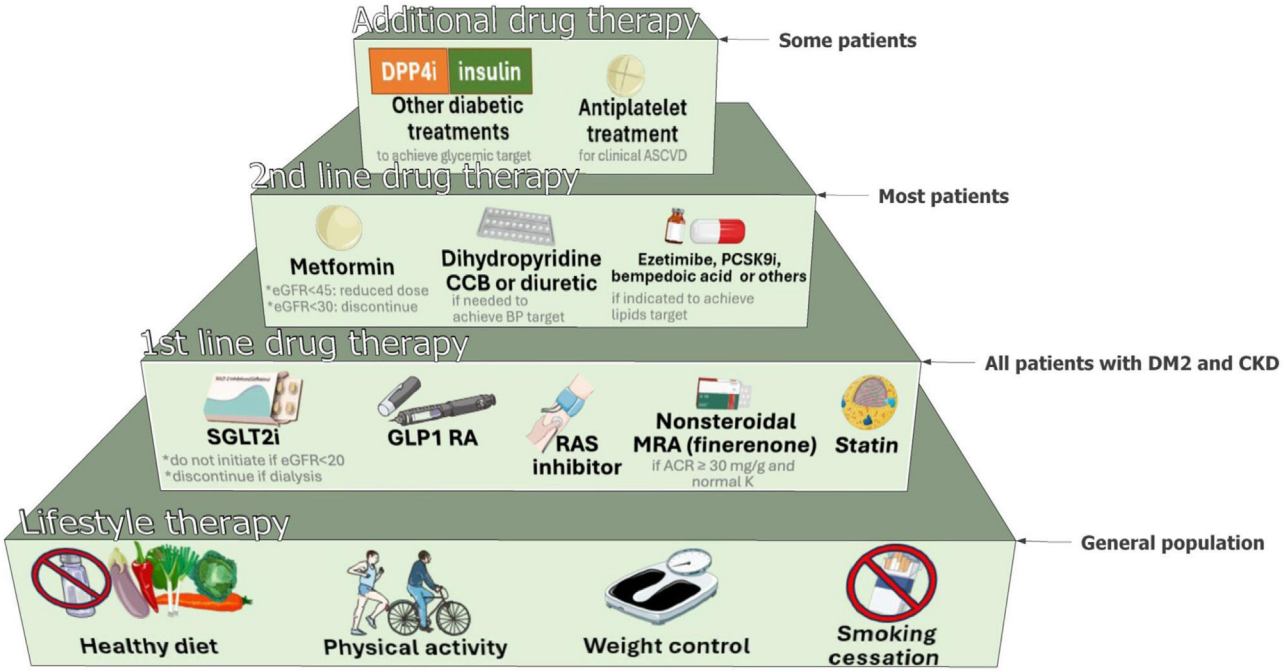

Fig. 2 – General management of patients with type 2 diabetes and chronic kidney disease.
Patients with diabetes and chronic kidney disease (CKD) should receive aholistic approach to avoid cardiovascular complications. This approach should considerlifestyle changes focused on nutrition with special attention to weight control, regular physical exercise, and smoking cessation, adding the use of first-line drugs, according to the clinicalcharacteristics of each patient and prioritizing those with proven benefit from the cardiorenal point of view. Glycemic control is based on insulin therapy in type 1 diabetes mellitus (T1D) Metformin can be used when the estimated glomerular filtration rate (eGFR) is greater than 30 ml/min and a combination of sodium-glucose cotransporter 2 inhibitors (SGLT2i) and GLP-1 RAs (especially semaglutide 1 mg once weekly) for type 2 diabetes mellitus (T2DM). per 1.73 m2, adjusting the metformin doses when eGFR would be between 30-45 ml/min per 1.73 m2. iSGLT2 should be initiated when the eGFR is greater than 20 ml/min per 1.73 m2 and continued until starting treatment with dialysis or transplant. Angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARBs) should be first-line drugs for hypertension when albuminuria is present. Otherwise, dihydropyridine calcium channel blockers (CCBs) or a diuretic may also be considered. All three classes are often required to achieve blood pressure (BP) goals. Adequate control of lipids with different pharmacological groups is crucial, and the use of statins is recommended for most patients with T1D or T2D and CKD. A nonsteroidal mineralocorticoid receptor antagonist (ns-MRA) such as finerenone may be added to the first-line treatment for cases with T2DM and high risks of CKD progression and cardiovascular events, depending on the patient's albuminuria (>30mg/g). Depending on the patient's characteristics, different pharmacological groups increase the therapeutic arsenal for improving the metabolic control of patients, including dipeptidyl peptidase-4 inhibitors (DPP-4i) or insulin. Other additional therapies, such as steroidal mineralocorticoid receptor antagonists, may also be used to achieve BP targets if potassium (K) levels allow it. Aspirin should generally be used for life for secondary prevention in patients with established cardiovascular problems and may be considered in primary prevention in those at high risk of atherosclerotic cardiovascular problems (ASCVD). Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ACR, albumin-creatinine ratio; ARBs, angiotensin II receptor blockers; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CCB, calcium channel blocker; CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MRA, mineralocorticoid receptor antagonist; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RAS, renin-angiotensin system; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

patients with diabetes, hypertension, and albuminuria and that these medications be titrated to the highest approved tolerated dose (Tables S4.1–3).

Strength of recommendation: 1A

Rationale: The cornerstone of CKD management in patients with T2D has been the use of renin-angiotensin system inhibitors (RAS). Several randomized trials demonstrated the reduction in CKD progression and the risk of kidney outcomes in high-risk subjects with moderately or severely increased albuminuria.

The IRMA-2 (Irbesartan in Patients With Type 2 Diabetes and Albuminuria)[88] and the INNOVATION (The Incipient to Overt: Angiotensin II Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy)[89] clinical trials were designed to test whether RAS blockade reduced the risk of progression of CKD in diabetes, defined as the development of

severely increased albuminuria (uACR > 300 mg/g). These studies enrolled patients with T2D and moderately increased albuminuria (uACR between 30 and 300 mg/g). The IRMA-2 study showed that treatment with irbesartan, an angiotensin-receptor blocker (ARB), was associated with a dose-dependent reduction in the risk of progression of CKD. The highest dose of 300 mg/day was associated with an almost three-fold risk reduction at two years of follow-up, a result that was independent of the blood pressure-lowering effect of irbesartan. On the other hand, a lower transition rate to overt nephropathy with respect to placebo after one year of follow-up was observed in the INNOVATION trial with the ARB telmisartan. In this study, the beneficial effect of telmisartan in slowing progression to overt nephropathy was also independent of blood pressure reduction with telmisartan.

Regarding the benefit of RAS blockade in patients with severely increased albuminuria, this was tested in two clinical trials that enrolled patients with urine albumin excretion ≥ 300 mg/day. In the RENAAL trial (The Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist losartan),[72] 1513 patients were randomly assigned to receive losartan or placebo once daily, along with conventional antihypertensive therapy as needed (excluding ACEi and ARB). The primary composite endpoint of doubling of serum creatinine concentration, end-stage kidney disease, or death was reduced by 16% in patients under treatment with losartan according to the intention-to-treat analysis ($P = 0.02$), an effect that remained after adjustment for blood pressure. The individual components of the primary composite endpoint that assessed the progression of kidney disease showed a significant benefit, with a reduction in the risk of doubling of serum creatinine concentration by 25% ($P < 0.01$) and in the risk of end-stage kidney disease by 28% ($P = 0.002$) in the losartan group compared to the placebo group. In addition, among the patients who continued to receive their assigned study treatment according to the per-protocol analysis, losartan conferred a 22% reduction in the risk of the primary composite endpoint ($P < 0.01$).[90]

Unlike RENAAL, the Irbesartan Diabetic Nephropathy Trial (IDNT) included an active comparator in addition to a placebo. This study recruited 1715 patients with T2D aged between 30 and 70 years, with hypertension and urinary protein excretion ≥ 900 mg/24 h, who were randomized to receive treatment with irbesartan, amlodipine, or placebo.[74] The primary endpoint was the composite of doubling of the baseline serum creatinine, the onset of ESRD (initiation of dialysis, kidney transplantation, or a serum creatinine concentration ≥ 6.0 mg/dL), or death from any cause. The relative risk of the primary endpoint in the placebo and amlodipine groups did not differ significantly. However, treatment with irbesartan was associated with a 20% lower risk of the primary composite endpoint than the placebo group ($P = 0.02$) and 23% lower than that in the amlodipine group ($P = 0.006$). The risk of doubling of serum creatinine concentration was 33% lower in the irbesartan group than in the placebo group ($P = 0.003$) and 37% lower in the irbesartan group than in the amlodipine group ($P < 0.001$). The relative risk of ESRD in patients receiving irbesartan was 23% lower than that in both other groups ($P = 0.07$ for both comparisons). These differences were independent of the blood pressure reached. The serum creatinine concentration increased 24% more slowly in the irbesartan group than in the placebo group ($P = 0.008$) and 21% more slowly than in the amlodipine group ($P = 0.02$).

The evidence does not demonstrate proven differences in outcomes or superior efficacy when comparing ACEi to ARB treatment. Thus, either agent can be used when treating patients with T2D and CKD, and the choice between ACEi and ARB will depend on other factors (patient preferences, cost, side-effect profile, etc.).[91,92]

Recommendation 4.3. Patients with T2D, an eGFR ≥ 25 ml/min/1.73 m^2, and increased albuminuria (uACR > 100 mg/g) on a stable maximal tolerated dose of RAS inhibitors should be treated with a GLP1RA with proven kidney benefit (Table S4.8).

Strength of recommendation: 1A

Rationale: There is new evidence for the kidney-protective properties of the GLP1RA semaglutide. In a post hoc analysis of the SUSTAIN 6/PIONEER 6 trials including pooled data from 6480 participants at high cardiovascular risk, there was a significant difference in the estimated treatment effect (semaglutide versus placebo) on eGFR slope: 0.59 ml/min/1.73 m^2 (95% CI: 0.29–0.89).[56,93] This effect was numerically largest in subjects with an eGFR between 30 and 60 ml/min per 1.73 m^2 [1.06 ml/min/1.73 m^2 (95% CI: 0.45–1.67)], but without significant interaction for treatment effect by subgroup.

This suggestion that semaglutide may reduce the rate of eGFR decline and have kidney-protective benefits has been evaluated in a dedicated clinical trial investigating the effects of once-weekly subcutaneous semaglutide (1 mg) in a population of patients with T2D and CKD at high risk of kidney disease progression. The FLOW study[59] that prematurely stopped after the interim analysis demonstrated efficacy after enrolling 3533 adults with T2D and kidney disease (defined by an eGFR of 25–75 ml/min/1.73 m^2, with a uACR of greater than 300 to less than 5000 mg/g if the eGFR was ≥50 ml/min/1.73 m^2 or a uACR > 100 and <5000 mg/g if the eGFR was between 25 and less than 50 ml/min/1.73 m^2) and a stable maximal labeled dose or the maximal dose without unacceptable side effects of RAS inhibitors.

The results demonstrated a 24% relative risk reduction of the primary composite outcome in the semaglutide group with respect to the placebo group (HR = 0.76; 95% CI: 0.66–0.88; $P = 0.0003$), with similar results for a composite of the kidney specific components of the primary outcome (HR = 0.79; 95% CI: 0.66–0.94). In addition, there were three key confirmatory secondary outcomes, which were assessed using a prespecified hierarchical testing approach: the annual rate of change in eGFR from randomization to the end of the study (total eGFR slope); a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes (MACE – major adverse cardiovascular events); and death from any cause. All the results for these confirmatory outcomes favored semaglutide: the total eGFR slope showed a lower reduction of 1.16 ml/min/1.73 m^2/year ($P < 0.001$); the risk of MACE was 18% lower (HR = 0.82; 95% CI: 0.68–0.98; $P = 0.029$); and the risk of death from any cause was 20% lower (HR = 0.80; 95% CI,

0.67–0.95; $P = 0.01$).

Recommendation 4.4. We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for patients with T2D, an eGFR ≥ 25 ml/min/1.73 m^2, normal serum potassium concentration (K ≤ 5.1 mmol/L), and albuminuria (uACR ≥ 30 mg/g) despite the maximum tolerated dose of RAS inhibitor (Table S4.6).

Strength of recommendation: 1A

Rationale: A nonsteroidal MRA can be added to first-line therapy for patients with T2D and high residual risk of kidney disease progression, as evidenced by persistent albuminuria (uACR ≥ 30 mg/g). The choice of a nonsteroidal MRA should prioritize agents with documented kidney or cardiovascular benefits. Finerenone is currently the only nonsteroidal MRA with proven clinical kidney and cardiovascular benefits.

The initial evidence for the clinical effectiveness of finerenone in improving kidney function and slowing the worsening of CKD comes from the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial.[77] In this phase 3, randomized, double-blind, multicenter, placebo-controlled trial, 5734 adults with T2D and CKD were randomly assigned to receive finerenone or a placebo. Eligible patients had an eGFR of between 25 and less than 60 ml/min/1.73 m^2, a uACR of between 30 and less than 300 mg/g, and diabetic retinopathy, or they had an eGFR of between 25 and less than 75 ml/min/1.73 m^2, a uACR of 300–5000. All the participants were treated with optimized RAS blockade before randomization. The primary outcome was the time to the first event of a composite endpoint consisting of a sustained decrease of at least 40% in the eGFR from baseline over at least four weeks, the onset of kidney failure (defined as an eGFR of less than 15 ml/min/1.73 m^2 or ESKD (initiation of long-term dialysis (for ≥90 days) or kidney transplantation)), or renal death. Results showed that the incidence of the primary composite outcome was significantly lower in the finerenone group than in the placebo group (17.8% vs. 21.1%, respectively), resulting in an HR = 0.82; 95% CI: 0.73–0.93; $P = 0.001$. Additionally, the incidences of the primary outcome components were consistently lower with finerenone than with placebo.

Additional clinical evidence was provided by the FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease)[94] and FIDELITY (Finerenone in Chronic Kidney Disease and Type 2 Diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial Programme Analysis)[95] studies. The FIGARO study included adult patients with T2D and CKD stage 1 or 2 (eGFR ≥ 60 ml/min/1.73 m^2) with a uACR of 300–5000 mg/g or CKD stage 2–4 (eGFR 25–90 ml/min/1.73 m^2) with a uACR of between 30 and less than 300 mg/g. Similarly to FIDELIO-DKD, RAS blockade was optimized in all patients before randomization. The primary outcome was cardiovascular (a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure), whereas the first secondary outcome was a composite of a sustained decrease in the eGFR ≥ 40% from baseline, kidney failure, or death from kidney causes. A total of 7437 patients underwent randomization. The incidence of the primary outcome was significantly lower in the finerenone group (HR = 0.87; 95% CI: 0.76–0.98; $P = 0.03$), with the benefit driven primarily by a lower incidence of hospitalization for heart failure. The incidence of the main secondary outcome was 9.5% in the finerenone group and 10.8% in the placebo group (HR = 0.87; 95% CI: 0.76–1.01), although the difference did not reach statistical significance. Analysis of the components of the first secondary outcome showed an incidence of end-stage kidney disease of 0.9% in the finerenone group and of 1.3% in the placebo group (HR = 0.64; 95% CI: 0.41–0.99). The kidney composite outcome of kidney failure, a sustained decrease from baseline of at least 57% in the eGFR, or death from kidney causes occurred in 2.9% of patients in the finerenone group and in 3.8% in the placebo group (HR = 0.77; 95% CI: 0.60–0.99).

Lastly, the FIDELITY study was a prespecified pooled analysis from FIDELIO-DKD and FIGARO-DKD aimed to provide more robust estimates of finerenone efficacy and safety across the spectrum of patients with CKD and T2D. This study included a total of 13,171 subjects and showed that patients receiving finerenone had a lower risk for the composite cardiovascular outcome of time to cardiovascular death, nonfatal MI, nonfatal stroke or hospitalization for HF (HR = 0.86; 95%CI: 0.78–0.95) and the composite kidney outcome of time to first onset of kidney failure, sustained eGFR decrease ≥57% or renal death (HR = 0.77; 95%CI: 0.67–0.88). Among the components of the kidney outcome, a 20% reduction in the risk for ESKD (HR = 0.80; 95%CI: 0.64–0.99) was noted.

Recommendation 4.5. We suggest maintaining a protein intake of 0.6–0.8 g/kg (weight)/day for patients with diabetes and CKD not treated with dialysis (Table S4.12).

Strength of recommendation: 2C

Rationale: Early animal studies demonstrated that high protein intake contributes to the development of increased intraglomerular pressure and glomerular hyperfiltration, which in turn leads to tubulointerstitial damage and glomerulosclerosis.[96] On this basis, reduced dietary protein intake has been demonstrated to reduce glomerular hyperfiltration and slow progression of CKD compared to a standard dietary protein intake of 0.8 g/kg/day.[97–99] However, these studies mainly included patients with advanced CKD and subjects without diabetes,[100] while there is a lack of clinical studies that compare different levels of protein content in the diet in patients with diabetes and CKD. Although two meta-analyses show a small beneficial impact of low protein diet on eGFR decline,[101,102] the high heterogeneity of the studies (type of diabetes, stages of CKD, types of interventions, duration, and adherence to recommendations) does not make it possible for strong recommendations to be made. Thus, we consider it advisable to apply the KDIGO guidelines regarding daily protein intake to patients with diabetes and CKD not receiving dialysis (0.6–0.8 g/kg/day), whereas a dietary protein intake > 1.2 g/kg body weight per day should be advised for diabetic CKD patients receiving dialysis.[103]

Lastly, it is important to note the potential dangers of an excessive reduction in protein intake in people with diabetes to less than 0.6 g/kg/day. This protein restriction may result

in a decrease in quality of life, increasing risk for episodes of hypoglycemia, inadequate weight loss and malnutrition.

Table 4 summarizes the key points concerning the management of T2D patients with CKD.

Chapter 5: Antiplatelet or anticoagulant therapy in people with diabetes and CKD

Recommendation 5.1. Patients with T1D or T2D and CKD with established atherosclerotic cardiovascular disease should be treated with low-dose aspirin (75–100 mg/day) for secondary prevention.

Strength of recommendation: 1B

Recommendation 5.2. Dual antiplatelet therapy (with low-dose aspirin and a $P2Y_{12}$ inhibitor) is recommended after acute coronary syndrome or percutaneous coronary intervention, followed by single antiplatelet therapy with a duration determined by a multidisciplinary team based on the benefit-risk profile.

Strength of recommendation: 1B

Recommendation 5.3. In patients with T1D or T2D and CKD and a previous non-cardioembolic ischemic stroke or transient ischemic stroke, the long-term use of antiplatelet therapy to reduce the risk of recurrent stroke is recommended.

Strength of recommendation: 1C

Recommendation 5.4. Dual antiplatelet therapy (with low-dose aspirin and a $P2Y_{12}$ inhibitor) after acute non-cardioembolic ischemic stroke/transient ischemic attack in patients with T1D or T2D and CKD followed by single antiplatelet therapy should be considered.

Strength of recommendation: 2C

Recommendation 5.5. There is no clear evidence of a favorable benefit-risk profile of low-dose aspirin for primary prevention of atherosclerotic cardiovascular disease in patients with T1D or T2D and CKD stage 3 or higher to recommend its prescription.

Strength of recommendation: 2C

Rationale: Low-dose aspirin (75–100 mg/day) should be prescribed for secondary prevention of atherosclerotic cardiovascular disease among patients with diabetes and CKD and atherosclerotic cardiovascular disease, according to all guidelines and the available evidence.[104–108] The recent post hoc analysis of the ADAPTABLE trial among the subset of patients with diabetes showed that there were no differences in terms of efficacy and safety of low dose (81 mg/day vs. 325 mg/day) or type (enteric-coated vs. uncoated) of aspirin, although a reduction in bleeding with enteric-coated aspirin could not be excluded. In this study, patients with diabetes showed a higher risk of bleeding than nondiabetics, although no subanalysis according to the baseline kidney function was reported.[109]

Dual antiplatelet therapy (low-dose aspirin plus a $P2Y_{12}$ inhibitor) is recommended for patients after acute coronary syndrome or percutaneous coronary intervention as per clinical guidelines.[2,4,5] However, the optimal duration of dual antiplatelet therapy in patients with diabetes and CKD, especially among those with advanced CKD (eGFR < 30 ml/min/1.73 m^2), needs to be carefully evaluated as they are at higher risk of bleeding.[110,111] Patients with diabetes and CKD and reduced eGFR experience a higher risk of cardiovascular events after acute coronary syndrome or percutaneous coronary intervention,[110,112–114] as well as a higher risk of bleeding,[110,112–114] but few trials have analyzed the efficacy and safety of dual antiplatelet therapy in this population. In a post hoc analysis of the PLATO (Platelet Inhibition and Patient Outcomes) trial, which randomized patients with acute coronary syndrome to ticagrelor versus clopidogrel, ticagrelor reduced the incidence of the composite primary endpoint (cardiovascular death, myocardial infarction, or stroke within twelve months) consistently across subgroups of patients with diabetes and/or CKD, but with an increased absolute risk reduction in DM+/CKD+, while there was no increased risk of major bleeding with ticagrelor compared to clopidogrel in the subgroup of patients with DM+/CKD+.[114] In a post hoc analysis of the GLOBAL-LEADERS trial, the effects of one-month dual antiplatelet therapy followed by 23-month ticagrelor monotherapy versus twelve-month dual antiplatelet therapy followed by twelve-month aspirin alone were analyzed according to DM/CKD status in patients undergoing percutaneous coronary intervention. Among patients with DM+/CKD+, ticagrelor monotherapy was not associated with lower rates of all-cause death, new Q-wave myocardial infarction, or major bleeding complications. Nonetheless, it was associated with lower rates of the patient-oriented composite endpoint (composite of all-cause death, any stroke, site-reported myocardial infarction, and any revascularization), and net adverse clinical events (a combination of patient-oriented composite endpoint with Bleeding Academic Research Consortium type 3 or 5 bleeding events). However, the authors stated that these findings should be considered hypothesis-generating.[112] In a post hoc analysis of the Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention (TWILIGHT) trial, after three-month dual antiplatelet therapy with ticagrelor and aspirin post-percutaneous coronary intervention, event-free patients were randomized to either aspirin or placebo in addition to ticagrelor for twelve months. The authors concluded that in DM+/CKD+ patients, ticagrelor monotherapy reduced the risk of bleeding without significantly increasing ischemic events compared to ticagrelor plus aspirin. However, this population had numerically higher rates of ischemic events.[113] Similarly, the Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study (THEMIS) trial found that in patients with stable coronary artery disease and DM but no history of myocardial infarction or stroke, combining ticagrelor with aspirin lowered ischemic event risks. Nonetheless, an increase in bleeding complications offset this benefit. Despite the lack of interaction by eGFR, patients with reduced eGFR tended to derive lower benefits in terms of efficacy and an increased risk of bleeding.[115] In the subgroup of patients from the THEMIS trial who had undergone previous percutaneous coronary intervention, the combination of ticagrelor and aspirin was found to have a net clinical benefit. However, despite no significant interaction, the benefits were lower among those with CKD stage 3 or higher.[116]

In the Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54 (PEGASUS-TIMI 54) trial, adding ticagrelor to aspirin reduced the risk of recurrent ischemic events, including cardiovascular and coronary heart disease death in patients with DM and prior myocardial infarction, but the combination was also associated with a higher risk of TIMI major bleeding,[117] and no subanalysis was performed on kidney function. In the CHARISMA trial, patients with established atherosclerotic cardiovascular disease (symptomatic) or multiple risk factors for atherosclerotic disease (asymptomatic), but without active acute coronary syndrome, were randomly assigned to receive either clopidogrel plus aspirin or placebo plus aspirin. Patients with diabetes and nephropathy who received clopidogrel did not have an increased risk of bleeding, but they experienced a significantly higher risk of CV and overall mortality compared to the placebo group. This suggests that clopidogrel may be harmful in patients with diabetes and CKD.[118]

Similarly, in stroke prevention guidelines among patients with a recent non-cardioembolic stroke/transient ischemic attack, the dual antiplatelet therapy strategy with aspirin and clopidogrel is recommended for 21 days, while dual antiplatelet therapy for longer than three months is discouraged.[105,106,119] In The Acute Stroke or Transient Ischemic Attack Treated with Ticagrelor and ASA for Prevention of Stroke and Death (THALES trial) among patients with a mild-to-moderate acute non-cardioembolic ischemic stroke or transient ischemic attack who were not undergoing intravenous or endovascular thrombolysis, the risk of the composite of stroke or death within 30 days was lower with ticagrelor–aspirin than with aspirin alone, however there were no differences in incidence of disability between the two groups and severe bleeding was more frequent with ticagrelor. Furthermore, in the analysis of subgroups, the efficacy endpoint appeared to be negligible among patients with diabetes, and no analysis was performed on eGFR.[120]

Concerning the long-term secondary prevention of ischemic stroke in patients with diabetes and CKD, we found no evidence from randomized controlled trials, and we suggest following the guidelines for the general population recommending the use of antiplatelet agents to reduce the risk of stroke recurrence.[105,106]

Although some guidelines state that aspirin may be considered for primary prevention among high-risk individuals including patients with DM, based on the higher risk of atherosclerotic cardiovascular disease,[2,4,5] this should be balanced against their increased risk for bleeding, including platelet dysfunction associated with reduced eGFR.[121] The ASCEND (A Study of Cardiovascular Events iN Diabetes) trial randomized patients with diabetes and no evident cardiovascular disease to 100 mg daily aspirin or placebo. During a mean follow-up of 7.4 years, there was a significant 12% reduction in the primary efficacy endpoint but an increase in major bleeding events in the aspirin group, where most cases were gastrointestinal and others extracranial bleeding. Thus, it was concluded that the absolute benefits were largely counterbalanced by the bleeding hazard, with a number needed to treat and needed to harm (NNT/NNH) ratio of 0.8.[122] However, no post hoc analysis of this study stratified by the presence of CKD has been reported. Among patients with diabetes and CKD, there is no strong evidence for a favorable benefit-risk profile from results in post hoc analysis of randomized controlled trials. The Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) trial was a prospective, randomized, open-label trial that enrolled patients with T2D without a history of atherosclerotic cardiovascular disease ($n = 2539$). The primary endpoint was a composite of sudden death: death from coronary, cerebrovascular and aortic causes; nonfatal acute myocardial infarction; unstable angina; newly developed exertional angina; nonfatal ischemic and hemorrhagic stroke; transient ischemic attack; or nonfatal aortic and peripheral vascular disease. After adjusting several variables, low-dose aspirin did not significantly reduce the primary endpoint in patients with an eGFR < 60 ml/min/1.73 m^2,[123] which was confirmed in the ten-year follow-up of the study (JPAD2[124]) in the subset of patients with an eGFR < 60 ml/min/1.73 m^2. However, it increased the risk of gastrointestinal bleeding in the whole population. More recently, the International Polycap Study 3 (TIPS-3) randomized patients to aspirin (75 mg/day) or placebo in primary prevention, although aspirin did not reduce the rate of cardiovascular death, myocardial infarction, or stroke in the whole population. Patients with diabetes and those with eGFR < 60 ml/min/1.73 m^2 tended to show a benefit (although the p for interaction was nonsignificant, as the number of patients with reduced eGFR was only 17.2% of the population and no post hoc analysis was conducted on patients with diabetes and reduced eGFR).[125,126] Therefore, there is limited evidence for the benefit of low-dose aspirin in terms of efficacy and safety for the primary prevention of atherosclerotic cardiovascular disease in patients with diabetes and CKD stage 3 or higher.

One limitation of these studies is that patients with advanced CKD or on dialysis were excluded, limiting the generalization of the results to this population.

According to the new 2024 American Diabetes Association (ADA) guidelines, the combination of aspirin plus low-dose rivaroxaban should be considered in patients with diabetes and stable coronary artery disease and/or peripheral artery disease and low bleeding risk to prevent major adverse limb and cardiovascular events[104] based on the positive results of the COMPASS (patients with diabetes subgroup)[127] and VOYAGER-PAD[128] trials, despite the higher risk of bleeding with this combination. However, no data on efficacy and safety among patients with diabetes and CKD stage 3 or higher have been reported. Still, no interaction in terms of effectiveness and safety by reduced eGFR or diabetes status was observed in the original COMPASS trial,[129] but there was a tendency to a lower benefit in patients with diabetes, as well as a higher risk of bleeding among patients with diabetes and patients with reduced eGFR in the VOYAGER PAD trial.[128] Furthermore, patients with CKD stage 5 or 5D were excluded from these trials, limiting the extrapolation of the results to this subgroup of patients with diabetes and CKD.

Recommendation 5.6. Patients with T1D or T2D and CKD with non-valvular atrial fibrillation should preferably be treated

with direct oral anticoagulants versus vitamin K antagonists in patients with CKD stages 1–4 (dabigatran up to stage 3b).

Strength of recommendation: 1B

Rationale: Atrial fibrillation is the most common arrhythmia worldwide and substantially increases the risk of stroke and thromboembolic events.[130] Both DM and CKD are associated with an increased risk of developing atrial fibrillation as compared to the general population.[130–132] Furthermore, the presence of DM and/or CKD in patients with atrial fibrillation increases the risk of thromboembolic events,[133–136] as well as mortality and bleeding risks.[136,137]

The most common score used to estimate the thromboembolic risk and indication for oral anticoagulation is the CHA_2DS_2-VASc,[130] and DM is one of the score items, therefore most patients with diabetes and CKD will indicate oral anticoagulation. The risk of bleeding under anticoagulation is usually estimated with the HAS-BLED score that includes kidney dysfunction as an item.[130]

There are currently two classes of commercially available oral anticoagulants: vitamin K antagonists (warfarin, acenocoumarol, etc.) and direct oral anticoagulants (apixaban, rivaroxaban, edoxaban, and dabigatran). CKD affects the bioavailability and pharmacokinetics of direct oral anticoagulants since they are all, at least partially, excreted by the kidneys (the renal clearance of dabigatran is around 80%, of edoxaban 50%, of rivaroxaban 33%, and of apixaban 27%) and may require dose adjustments in patients with reduced eGFR. Its indication is not recommended in patients with CKD stage ≥ 4 (dabigatran) or CKD stage 5 (edoxaban, rivaroxaban, or apixaban).[138] No clinical trials evaluated its use in patients with diabetes and CKD. However, post hoc analysis or metanalysis of RCTs has demonstrated the efficacy and safety of direct oral anticoagulants versus vitamin K antagonists in patients with diabetes and the CKD population, and both metanalyses found a lower risk of thromboembolic events, intracerebral hemorrhage and death, with similar risk in major bleeding versus vitamin K antagonists until advanced stages of CKD.[136,139]

Furthermore, vitamin K antagonists show a shorter time in therapeutic range in CKD that worsens as the disease progresses, which is associated with a greater risk of thromboembolic and hemorrhagic events.[138,140] In addition, data derived from RCTs with dabigatran and rivaroxaban suggest that direct oral anticoagulants could have a benefit in terms of reducing the progression of CKD.[38,39] In CKD stages 5 and 5D, direct oral anticoagulants and vitamin K antagonists are not recommended[130] because the efficacy and safety in this population are based on a scarce number of RCTs and guidelines give no clear recommendations in this setting.[138] Furthermore, direct oral anticoagulants are not indicated in patients with valvular arrhythmias and/or heart valve prostheses.[130]

Recommendation 5.7. Patients with T1D or T2D and CKD with venous thromboembolism should preferably be treated with direct oral anticoagulants over vitamin K antagonists in patients with CKD stages 1–4 (dabigatran up to stage 3b).

Strength of recommendation: 2C

Rationale: Venous thromboembolism, which includes deep vein thrombosis and pulmonary embolism (PE), is also an indication of anticoagulation.[141,142] There is an increased risk of venous thromboembolism both in patients with diabetes[143] as well as in those with CKD,[144] where the risk of venous thromboembolism increases as kidney function declines.[144] Furthermore, diabetes mellitus and CKD are risk factors for recurrent venous thromboembolism.[44,45] Among deep vein thrombosis, unprovoked deep vein thrombosis refers to venous thrombosis in the absence of identifiable risk factors. Similarly, provoked deep vein thrombosis occurs in the presence of such risk factors, which can be further classified as transient or persistent. The provoked or unprovoked nature of deep vein thrombosis, as well as the chronicity of any provoking risk factors (transient or persistent), has significant prognostic and treatment implications, as recurrence risk and anticoagulation regimens differ accordingly.[141] Deep vein thrombosis requires anticoagulation with unfractionated heparin, fondaparinux, low molecular weight heparins, direct oral anticoagulants, or vitamin K antagonists. Among direct oral anticoagulants, apixaban and rivaroxaban can be started without initial parenteral anticoagulation.[141]

Among patients with pulmonary embolism, those with high risk require treatment with unfractionated heparin in the acute phase. Nonetheless, among those with intermediate or low risk when oral anticoagulation is indicated, a direct oral anticoagulant (dabigatran, rivaroxaban, apixaban, or edoxaban) is preferred over vitamin K antagonists.[41] Direct oral anticoagulants provide similar efficacy and a lower risk of major bleeding and intracranial hemorrhage or fatal bleeding than low molecular weight heparins and vitamin K antagonists; the benefit was also observed in the population of reduced creatinine clearance[145,146] and although the trials were performed in patients with creatinine clearances up to 25–30 ml/min/1.73 m^2, there is evidence for some of them of its safety in patients with creatinine clearances up to 15 ml/min/1.73 m^2.[147] However, direct oral anticoagulants are not recommended in patients with venous thromboembolism and advanced CKD, or antiphospholipid syndrome, or who are pregnant or lactating.[142]

The optimal duration of oral anticoagulation will depend on the type of deep vein thrombosis (provoked or unprovoked), the duration of the risk factor (transient or persistent), and the risk of recurrence of venous thromboembolism.[141,142] However, no data on patients with diabetes and CKD and reduced eGFR were found in this review.

Conclusions

Patients with diabetes and CKD should be treated according to the most up-to-date recommendations.

Most of this guideline is based on high-quality evidence. Especially for pharmacological treatments, many data from randomized clinical trials have been evaluated.

The main limitations of this guideline are that research in the field of diabetes is still active and additional data on existing and novel approaches are awaited. Another limitation is that we have not covered the chapter on dyslipidemia or pregnancy, as this was not foreseen in the initial approach, so we recommend referring to the published guidelines of other scientific societies. In addition, high cost and other resource

constraints in health systems will limit the application of some recommendations across individuals and populations.

Clinical Practice Guidelines will continue to evolve. It is likely that new guidelines focused on the diagnosis and treatment of people with diabetes and CKD will be needed in the near future.

Authorship

NM participated in research design, performance of research, data analyses and writing the paper. LO participated in the performance of research, data retrieval and analyses and writing the paper. AMC, MG, JLG, MJS, BFF, MQ, DRE and JFN participated in data retrieval and writing the paper. CG, PG, JG, PM, MJP, NS and RS participated in data retrieval and analyses. All authors approved the final version of the article. JFNG, AMC, JLG, MJS and BFF equally contributed to the concept and design.

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Conflict of interest

AMC has received honoraria as a speaker from Bayer, Boëhringer-Ingelheim, Lilly, Novo-Nordisk, Esteve and Merck-Sharp-Dhôme, and has participated in advisory boards from Boëhringer-Ingelheim, Lilly and Merck-Sharp-Dhôme. JLG has been an advisor on scientific boards for AstraZeneca, Bayer and Novo Nordisk; lectures for AstraZeneca, Boehringer Ingelheim, Esteve, Bayer, Eli Lilly and Company, Bayer, Astellas and Novo Nordisk and research activities for AstraZeneca. MS received grants or contracts from Boehringer, ISCIII, and Marató TV3; honoraria for lectures from NovoNordisk, Jansen, Boehringer, Mundipharma, AstraZeneca, Ingelheim Lilly, Vifor, ICU Medical, Fresenius, and Travere Therapeutics; support for attending meetings from Travere; participation on a data safety, monitoring board or advisory board from NovoNordisk, Jansen, Boehringer, Mundipharma, AstraZeneca, Ingelheim Lilly, Vifor, ICU Medical, Bayer, GE Healthcare, and Travere Therapeutics. MS has the following leadership or fiduciary roles: SEC board member, SEN board member, former ERA board member, former ASN Board News, former ERA-EDTA SAB, former ERA council member, Western Europe ISN co-chair. BFF has received grants from Esteve and AstraZeneca and consultancy or speaker fees or travel support from AstraZeneca, Bayer, Menarini, Novo-Nordisk, Boehringer, Lilly, Amgen and Mundipharma. BFF is editor for Nefroplus and CME chair of the European Renal Association. JJGM has the following financial relationships: advisor on scientific boards for AstraZeneca, Bayer, Janssen Pharmaceuticals, Eli Lilly and Company, Menarini and Novo-Nordisk; lectures for Abbott, Amarin, AstraZeneca, Boehringer Ingelheim Pharmaceuticals Inc, Janssen Pharmaceuticals, Eli Lilly and Company, Menarini, Mundipharma Pharmaceuticals, Novo-Nordisk and Roche Pharma, and research activities for AstraZeneca, Eli Lilly and Company, Mundipharma Pharmaceuticals and NovoNordisk. MPM has received consultancy, speaker fees or travel support from Astellas, AstraZeneca, Boehringer Ingelheim, CSL Vifor, Lilly, Menarini and Novo Nordisk. RS has received consultancy or speaker fees or travel support from AstraZeneca, Boehringer Ingelheim, Menarini, Novartis, NovoNordisk and Vifor Pharma. CGC has received travel and congress fees support from AstraZeneca, Esteve, NovoNordisk, Boehringer Ingelheim Lilly, Astellas, Otsuka, Novartis, Astellas, and Baxter; has given scientific lectures and participated in advisory boards organized by AstraZeneca, Boehringer Ingelheim Lilly, Mundipharma, Esteve, Otsuka, and NovoNordisk; and she is part of the Clinical Kidney Journal Editorial Board, Kidney News Editorial Board, and the Spanish Young Nephrologist Group Board (Spanish Society of Nephrology). PM has received consulting and/or speaker fees from CSL Vifor, Fresenius Kabi, Abbot, Baxter, Palex and Medtronic. JFNG has received grants from Abbvie, Bionet Medical, Boehringer Ingelheim, Sanofi-Genzyme, Shire and CSL Vifor, and consultancy or speaker fees or travel support from AstraZeneca, Amgen, Bayer, Bionet Medical, Boehringer Ingelheim, Eli Lilly, Esteve, GlaxoSmithKline, Janssen, Menarini, MSD, Mundipharma, Novartis, Novo-Nordisk, Sanofi-Genzyme, Servier and CSL Vifor. JFNG is member of the Scientific Advisory Board of the European Renal Association. NS has the following financial relationships: advisor on scientific boards for AstraZeneca, Eli Lilly and Company, Menarini and Novo-Nordisk; lectures for AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Menarini, Mundipharma Pharmaceuticals and Novo-Nordisk.

Information on the supplement

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.nefro.2024.11.002.

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