A review of the latest real-world evidence studies in diabetic kidney disease: What have we learned about clinical practice and the clinical effectiveness of interventions?

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A review of the latest real-world evidence studies in diabetic kidney disease: What have we learned about clinical practice and the clinical effectiveness of interventions?

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Abstract

Diabetic nephropathy, also known as diabetic kidney disease (DKD), remains a challenge in clinical practice as this is the major cause of kidney failure worldwide. Clinical trials do not answer all the questions raised in clinical practice and real-world evidence provides complementary insights from randomized controlled trials. Real-life longitudinal data highlight the need for improved screening and management of diabetic nephropathy in primary care. Adherence to the recommended guidelines for comprehensive care appears to be suboptimal in clinical practice in patients with DKD. Barriers to the initiation of sodium-glucose cotransporter-2 (SGLT2) inhibitors for patients with DKD persist in clinical practice, in particular for the elderly. Attainment of blood pressure targets often remains an issue. Initiation of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in routine clinical practice is associated with a reduced risk of albuminuria progression and a possible beneficial effect on kidney function. Real-world evidence confirms a beneficial effect of SGLT2 inhibitors on the decline of glomerular filtration, even in the absence of albuminuria, with a lower risk of acute kidney injury events compared to GLP-1RA use. In addition, SGLT2 inhibitors confer a lower risk of hyperkalaemia after initiation compared with dipeptidyl peptidase-4 inhibitors in patients with DKD. Data from a large population indicate that diuretic treatment increases the risk of a significant decline in glomerular filtration rate in the first few weeks of treatment after SGLT2 inhibitor initiation. The perspective for a global approach targeting multifaceted criteria for diabetic individuals with DKD is emerging based on real-world evidence but there is still a long way to go to achieve this goal.

KEYWORDS
diabetic nephropathy, empagliflozin, GLP-1, SGLT2 inhibitor

1 | INTRODUCTION

Diabetic kidney disease (DKD), also known as diabetic nephropathy, remains a huge challenge in clinical practice as this is the major cause of kidney failure worldwide.

It is estimated that approximately 30%–40% of patients with diabetes also have chronic kidney disease (CKD; Stages 1–4) and that approximately 35% of end-stage kidney disease (ESKD) cases are attributable to diabetes.[1] CKD in diabetes represents a severe complication with an increased risk of progression towards ESKD, dialysis or kidney transplantation but also an elevated risk of onset of cardiovascular events and increased cardiovascular mortality. A residual cardiovascular risk for patients with diabetes persists despite recommended treatments.[1] Therefore, international guidelines recommend the provision of comprehensive care with multifaceted targets and criteria.[2] This includes renin-angiotensin system (RAS) blockade, appropriate control of blood pressure (BP) and glycaemia, as well as the use of sodium-glucose cotransporter-2 (SGLT2) inhibitors and nonsteroidal mineralocorticoid receptor antagonists (MRAs) in cases of persistent albuminuria. A number of clinical trials have provided evidence on the benefits of some drugs or therapeutic strategies in DKD.[3–5] However, clinical trials do not answer all the questions raised in clinical practice and populations included in these randomized controlled trials (RCTs) may be less heterogenous than those included in real-life studies and thus are not totally representative of patients observed in clinical practice.[6] Therefore, real-world evidence provides complementary insights to those obtained from RCTs as well as sometimes confirmatory results to those observed in the RCT.

The aim of this review was to synthesize the latest real-world studies covering the period 2020–2024 among people with DKD. We considered observational studies based on clinical databases, registries, cohort and prescription medication databases. Based on this real-world evidence, we attempted to decipher the underlying clinical lessons and perspectives to improve the care of people with DKD.

2 | ADHERENCE TO RECOMMENDED GUIDELINES

The recommended strategy in people with DKD is a comprehensive care programme, targeting multifaceted criteria and using therapies which have been demonstrated to reduce the risk of adverse outcomes.[2,7] In addition, adequate control of known risk factors for CKD progression and cardiovascular events, such as BP, glycaemia, and lipids is advocated.[2,7]

The clinical benefit conferred by the attainment of multifactorial targets in people with DKD has been suggested by a few RCTs, which showed that a programme of intensive and structured care was associated with the attainment of more treatment targets and a lower rate of progression towards kidney failure, as well as decreased cardiovascular events or mortality.[8,9] In the Steno-2 Study, patients were subsequently followed observationally for a mean of 5.5 years and intensive therapy during the treatment period was associated with a subsequent lower risk of death from cardiovascular causes and of cardiovascular events over a total follow-up period of 13.3 years.[10] In Italy, the NID-2 interventional trial performed in 14 diabetology clinics showed that, in patients with type 2 diabetes and albuminuria in a primary prevention setting, intensive multifactorial therapy targeting the main cardiovascular risk factors (BP < 130/80 mmHg, glycated haemoglobin [HbA1c] <7%, low-density lipoprotein cholesterol <2.6 mmol/L, high-density lipoprotein cholesterol >1.0/1.3 mmol/L in men/women, total cholesterol <4.5 mmol/L) was associated with a lower incidence of cardiovascular events and all-cause death, compared with standard care.[11]

In real-world settings, some recent reports have shown that adherence to the international guidelines appears to be suboptimal in clinical practice in patients with CKD.[12] In the French CKD-REIN cohort of patients with DKD, only 80% of the patients with CKD Stages 3–4 were treated with an RAS inhibitor,[13] whereas the proportion was 98% in the patients included in the DAPA-CKD trial.[14] A German database analysis based on 134 395 patients with type 1 or type 2 diabetes showed that only 49% had albuminuria measured at least once a year. Measured glomerular filtration rate (GFR) and estimated glomerular filtration rate (eGFR) were obtained more often in type 2 (91%) than in type 1 diabetes (82%). Only 44% of those with type 1 diabetes and 49% of those with type 2 diabetes had both parameters measured, that is, underwent at least one eGFR and one albuminuria assessment.[15]

Furthermore, in those with microalbuminuria, only 24% of those with type 1 diabetes and 40% of those with type 2 diabetes received RAS inhibition treatment. In patients with macroalbuminuria/proteinuria, the rate was higher but still suboptimal (41% for type 1 and 48% for type 2 diabetes).[15] In a Finnish primary healthcare group, observational data showed that just over half of the study population (57%) had been prescribed RAS inhibition.[16]

In a US population of 39 158 adults with diabetes and CKD (mean age 70 ± 14 years) from the Center for Kidney Disease Research, Education, and Hope Registry, RAS inhibition was prescribed to 71% of patients.[17] Overall, 40.4% of patients with diabetes and CKD had an RAS inhibition prescription that lasted ≥90 days. Of those prescribed RAS inhibition at baseline, 51.4% persisted with treatment for ≥90 days. In those prescribed an SGLT2 inhibitor at baseline, 46.4% persisted for ≥90 days whereas 51.8% of those prescribed a glucagon-like peptide-1 receptor agonist (GLP-1RA) at baseline persisted for ≥90 days.[17] These results underscore that the prescription rates of recommended renoprotective treatments remain suboptimal and wane quickly in patients with diabetes and CKD.[17]

In a recent Swedish nationwide study, the proportion of patients with type 2 diabetes who were recommended treatment with an SGLT2 inhibitor or a GLP-1RA according to the recent guidelines was approximately 80%, underscoring that uptake of the guidelines in routine clinical practice remains limited.[18] A study performed in Korea showed that only 39% of patients with DKD who were eligible for SGLT2 inhibitors were treated with SGLT2 inhibitors in real-world clinical practice.[19] In that study, age > 65 years was associated with a lower than expected rate of initiation of SGLT2 inhibitor treatment

and appeared to be a major barrier to the initiation of SGLT2 inhibitors for patients with DKD.[19]

3 | BP CONTROL

Appropriate control of high BP is a cornerstone of the care of patients with DKD. The relationship between BP observed during an intervention trial and the development of cardiorenal events has been well documented.[20]

For patients with diabetes and CKD, the BP target usually recommended is <130/80 mmHg.[2] However, this recommendation for people with diabetes remains an expert opinion based on limited evidence, and the definition of BP therapeutic targets remains debated.[21] In 2010, the intervention ACCORD trial showed that, in patients with type 2 diabetes at high cardiovascular risk, a systolic BP (SBP) <120 mmHg provided no benefit in terms of cardiovascular risk when compared to SBP <140 mmHg.[22] A recent analysis from the Korean National Health Insurance System database with a 10-year follow-up showed that, in approximately 326 000 patients with type 2 diabetes (with a mean eGFR of 75 mL/min/1.73 m^2), compared with the group with SBP of 120–129 mmHg, the SBP category of 130–139 mmHg was associated with the lowest hazard ratio (HR) for major adverse cardiovascular events (MACE). An SBP > 160 mmHg was associated with the highest HR for MACE after adjusting for age, sex, smoking, body mass index, dyslipidaemia, HbA1c, eGFR, use of statins and RAS blockade.[23] Compared with the SBP category of 120–129 mmHg, the SBP categories <110 mmHg and 110–119 mmHg were associated with higher HRs for MACE in the fully adjusted model.[24]

Contrary to that observed for MACE and all-cause mortality, the lower the SBP, the lower the HR for renal events (defined as a composite of ESKD, doubling of serum creatinine and renal death). An SBP/diastolic BP (DBP) of 110–119/75–79 mmHg was associated with the lowest HR for renal events.[24] In that study, the higher the SBP, the higher the HR for renal events.[24]

A cohort study using the Korean National Health Insurance Service database including 2 262 725 subjects with type 2 diabetes mellitus showed a lower incidence of cardiovascular disease (CVD) for patients with diabetes with BP below 130/80 mmHg compared with those with a higher BP, but all-cause mortality increased if SBP was below 110 mmHg or DBP was below 75 mmHg.[25] It remains difficult to ascertain the BP threshold at which the renal and cardiovascular benefits are the highest; therefore, these findings suggest that BP targets and BP management should be individualized after considering comorbid diseases and that too low levels of BP should be avoided among patients with DKD.

Attainment of BP goals often remains an issue in real-world clinical practice. In the German diabetes registries dataset of 134 395 patients with diabetes (including 17 649 with type 1 diabetes), hypertension control (defined as SBP <130 mmHg) was 41% in type 1 and 68% in in type 2 diabetes patients aged 18–65 years. Hypertension control in those aged >65 years (SBP goal within a range of 130–139 mmHg) was 62% in type 1 and 68% in type 2 diabetes.[15]

4 | GLUCOSE CONTROL

Glucose control remains a matter of ongoing debate, with a personalized approach recommended taking into account age, hypoglycaemic risk and presence of comorbidities. KDIGO recommends an individualized HbA1c target range between <6.5% and <8.0%, with higher targets tolerated for those who have severe macrovascular complications, many comorbidities and elevated hypoglycaemia risk.[26]

Findings from real-world evidence studies showed that only a minority of patients with DKD attained HbA1c targets. In the German registry, only 43.5% of patients with type 2 diabetes reached the HbA1c target of <7.0%.[15] In the French CKD-REIN cohort, 49% of the patients with DKD (mean eGFR 33 mL/min/1.73 m^2) had an HbA1c below 7.0%.[13] In this cohort, approximately half of the subjects with DKD were treated with insulin.[27]

5 | ALBUMINURIA TESTING AND CONTROL

Albuminuria is a well-established marker of diabetic nephropathy. Albuminuria assessment is recommended once a year for patients with diabetes as a screening tool for the presence of diabetic nephropathy. Despite these recommendations, albuminuria measurement is often neglected in the management of patients with diabetes.[28] Real-life longitudinal data based on the results of laboratory tests performed in 165 laboratories in France from 2015 to 2022 showed in a total of 246 225 patients with diabetes that the average number of urinary albuminuria/creatinine (UACR) measurements per patient was 0.34/year (median: 0.24), while GFR was estimated 1.73 times/year and HbA1c 1.55 times/year.[27] Among the 16 695 patients with elevated albuminuria (>30 mg/g), only 8564 (51.3%) had a follow-up UACR measurement with an average time interval of 363 days between the two measures.[27] These findings highlight the need for improved screening and management of diabetic nephropathy in primary care.

A large national cohort of patients with type 2 diabetes in the United States showed a low rate of albuminuria testing, along with a substantial delay before the initiation of RAS inhibition.[29] In an observational study analysing 1260 patients with DKD in France (mean eGFR 33 mL/min/1.73 m^2), 39% of them had a UACR >300 mg/g, despite the treatments prescribed, underscoring the need to address more intensively albuminuria in patients with DKD including those already under RAS inhibition.[13]

6 | RELATIONSHIP BETWEEN ATTAINMENT OF TARGETS AND CARDIORENAL OUTCOMES

As shown in Figure 1, in a cohort of 1260 patients with DKD, before the introduction of SGLT2 inhibitors to the French market (2020), the attainment of at least two nephroprotection targets (BP <130/80 mmHg, RAS inhibition, HbA1c <7.0%, and UACR

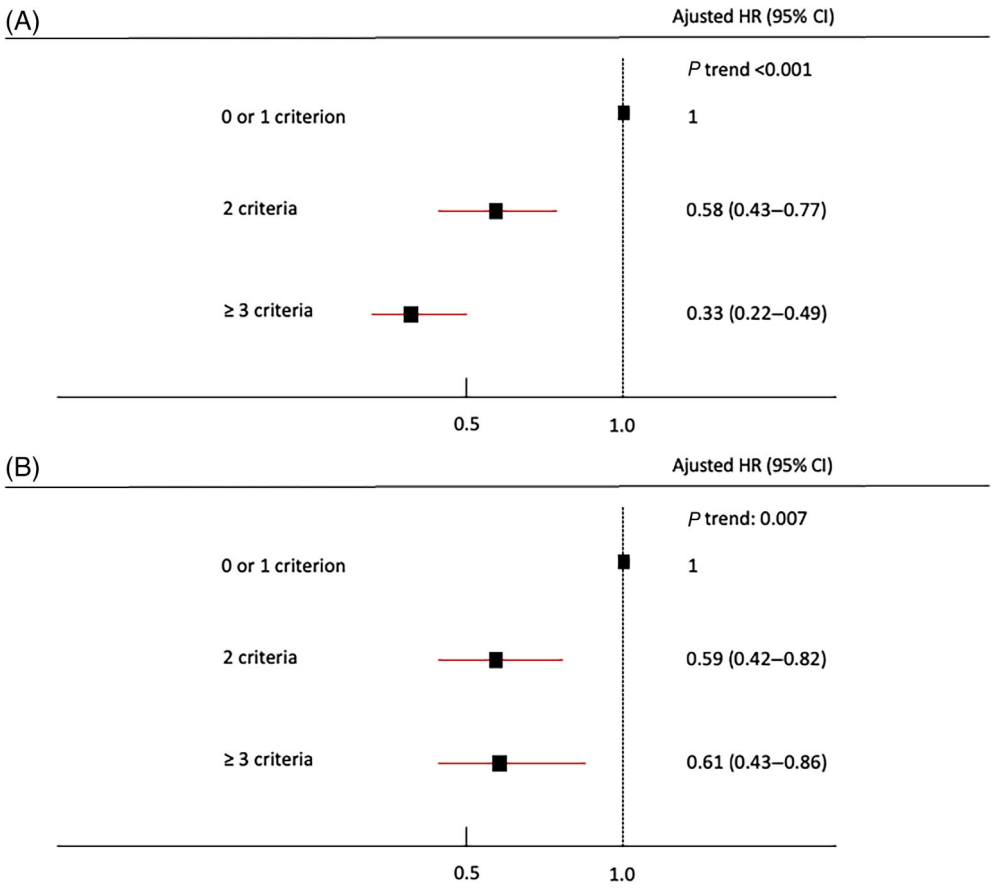

FIGURE 1 Forest plot of the adjusted hazard ratios (HRs) for kidney failure with replacement therapy (A) and total mortality (B) according to the number of nephroprotection targets (urinary albuminuria/creatinine <300 mg/g; renin-angiotensin blockade; blood pressure <130/80 mmHg; glycated haemoglobin < 7.0%) attained in 1260 diabetic patients with chronic kidney disease. HRs adjusted for age, sex, educational level > 12 years, current smoking, estimated glomerular filtration rate, low-density lipoprotein cholesterol, body mass index, prescription of aspirin or another platelet antiaggregant, statin, and glucagon-like peptide-1 receptor agonists. Adapted from reference.[13]

<300 mg/g) was consistently associated with a lower risk of cardiorenal events, ESKD, MACE, and all-cause mortality over a 5-year follow-up, as compared with the attainment of zero or one target.[13] These findings emphasize the importance of combining BP control, glycaemic control, and RAS inhibition in order to improve the cardiorenal prognosis, notably in those with severe albuminuria.[13]

7 | CARDIOVASCULAR OUTCOMES IN PATIENTS WITH DKD

A large prospective cohort of 19 025 Chinese patients with type 2 diabetes (the Hong Kong Diabetes Biobank) recently showed that decreased eGFR without albuminuria was associated with an increased risk of hospitalization for heart failure (HR 3.08, 95% confidence interval [CI] 1.82–5.21) when compared with patients with diabetes but without CKD.[30] However, the risk of CVD (coronary heart disease, stroke, peripheral vascular disease) was not significantly greater for those without albuminuria (HR 1.14, 95% CI 0.88–1.48) in comparison to those without kidney disease.[30] Decreased eGFR without albuminuria was also associated with an increased risk of all-cause mortality (HR 1.59, 95% CI 1.04–2.44), with this risk being mainly concentrated in those with baseline eGFR <30 mL/min/1.73 m^2.[30] In that Hong Kong registry study, the highest risk was observed for diabetic subjects with both albuminuria and decreased eGFR in terms of hospitalization for heart failure (HR 5.50, 95% CI 3.63–8.34); CVD (HR 1.47, 95% CI 1.23–1.76) or death (HR 3.26, 95% CI 2.43–4.38) in comparison to those without kidney disease.[30] The recent real-world EMPRISE study analysing new users showed cardiovascular benefits for empagliflozin initiators compared with either DPP-4 inhibitors[31] or GLP-1RA initiators.[32] It should be noted that, in that study, only a minority of patients had CKD at baseline (baseline eGFR was approximately 80 mL/min/1.73 m^2).[32]

8 | REAL-WORLD EVIDENCE ON MRAS

It has been suggested that MRAs exert renoprotective effects.[33,34] RCTs have shown an antiproteinuric effect of MRAs in CKD patients concomitantly treated with RAS blockers and SGLT2 inhibitors.[35] Furthermore, in a recent RCT of patients with type 2 diabetes, a nonsteroidal selective MRA, finerenone, reduced the risk of severe renal outcomes despite an increased risk of hyperkalaemia.[4] However, real-world evidence about MRA use has been limited in CKD to date.

A retrospective observational study including 3195 CKD patients with an eGFR of 10–60 mL/min/1.73 m^2 assessed evolution towards kidney failure according to the use of MRAs (spironolactone, eplerenone, or potassium canrenoate). The rate of onset of kidney failure with replacement therapy was significantly lower in patients treated with MRAs than in those treated without MRAs (HR 0.72, 95% CI

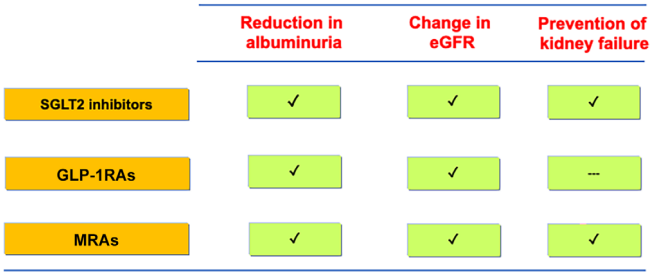

FIGURE 2 Summary of the data from the real world on the renoprotective effects of sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and mineralocorticoid receptor antagonists (MRAs). eGFR, estimated glomerular filtration rate.

0.53–0.98). In additional analyses, MRA use was significantly associated with a lower risk of progression of proteinuria (HR 0.75, 95% CI 0.59–0.95). Similar results with improved kidney outcomes were observed for the subgroup of 1318 patients with diabetes and CKD.[36]

The 2022 KDIGO guidelines recommend the introduction of non-steroidal MRA with proven kidney or cardiovascular benefit for diabetic patients with cardiorenal disease and albuminuria (UACR >30 mg/gCr) despite adequate RAS inhibitor therapy if they have an eGFR >25 mL/min/1.73 m^2 and normal serum K concentrations (level of evidence 2A).[26]

9 | REAL-WORLD EVIDENCE ON GLP-1RAS

The GLP-1RA class of drugs have shown potential renoprotective effects in some cardiovascular outcome trials.[37–39] Liraglutide, semaglutide and dulaglutide were all associated with significant reductions in nephropathy (defined as new-onset macroalbuminuria or doubling of serum creatinine, an eGFR of ≤45 mL/min/1.73 m^2, the need for renal replacement therapy, or renal death) compared with placebo in the LEADER[37]; SUSTAIN-6[38] and REWIND[39] studies, respectively.

Data on the effects of GLP-1RA treatment on kidney function and damage in real-world settings are still limited. Nevertheless, new evidence has recently been reported on this topic Figure 2).

A retrospective cohort analysis of 2.2 million people with type 2 diabetes receiving insulin, approximately 20% of whom had CKD, assessed the relationship of GLP-1RA treatment with the 5-year risk of several cardiovascular and renal endpoints.[40] In that analysis, treatment with a GLP-1RA was associated with a reduced risk of CKD over 5 years when compared with propensity-matched controls who received neither a SGLT2 inhibitor nor a GLP-1RA (HR 0.90, 95% CI 0.88, 0.92).[40]

An Israeli study based on the Maccabi Healthcare Services database assessed the association of GLP-1RA initiation with long-term kidney outcomes. Adults with T2D treated between 2010 to 2019 with at least two glucose-lowering agents who initiated GLP-1RA treatment were compared to those who initiated basal insulin with propensity-score matching. There was no significant difference in the HRs for the composite kidney outcome for GLP-1RA versus basal insulin (HR 0.96, 95% CI 0.82–1.11) in the intention-to-treat analysis. In an as-treated analysis, the HR was reduced (HR 0.71, 95% CI 0.54–0.95).[41] There was a significant reduction in the risk of onset of macroalbuminuria: HR 0.87 (95% CI 0.75–0.997) and 0.80 (95% CI 0.64–0.995) in the intention-to-treat and as-treated analyses, respectively. The use of a GLP-1RA was associated with a less steep eGFR slope compared with basal insulin in the as-treated analysis (mean annual between-group difference of 0.42 mL/min/1.73 m^2/year [95% CI 0.11–0.73]; $p = 0.008$).[41] That study provides evidence that initiation of a GLP-1RA in a real-world setting is associated with a reduced risk of albuminuria progression and a possible beneficial effect on kidney function loss in patients with T2D and mostly preserved kidney function.

A single-centre retrospective observational study conducted in 88 T2D Japanese patients treated with oral semaglutide showed improvements in cardiovascular risk factors.[42] Furthermore, in that study there was a trend to a decrease in the UACR after both 3 and 6 months, suggesting potential positive effects of GLP-1RA treatment on DKD.[42]

There is no direct trial comparison of the relative renal benefits of SGLT2 inhibitor versus GLP-1RA users. Therefore, real-world evidence is of interest despite the possible existence of an indication bias relating to the specific indication or clinical profile of each class in type 2 diabetes. In the Swedish nationwide observational study in 21 745 subjects with a mean eGFR of 91.3 mL/min/1.73 m^2, the incidence rate of the renal composite was nonsignificantly different in the group treated with a GLP-1RA compared to the group treated with an SGLT2 inhibitor.[43] Using a linkable Italian administrative health database, Baviera et al. showed that GLP-1RA initiators had a twofold risk of being hospitalized for renal disease compared to SGLT2 inhibitor initiators.[44] This result could be attributable to a higher prevalence of patients with reduced renal function in the GLP-1RA-treated group, which may be related to the more restricted indications for initiation of SGLT2 inhibitors in the presence of CKD until 2019 in Italy.[44]

In a large meta-analysis of observational studies, there was no significant difference in the risk of kidney failure between SGLT2 inhibitor and GLP-1RA treatment (HR 0.93, 95% CI 0.80–1.09).[45]

10 | REAL-WORLD EVIDENCE ON THE CLINICAL EFFECTIVENESS OF SGLT2 INHIBITORS

Results from real-world studies and registries have provided additional data based on a large number of patients. These findings confirm that the benefits of SGLT2 inhibitor therapy on kidney function seen in most randomized trials are translatable to routine clinical practice (Table 1).[46–51]

Early studies showed a reduction in albuminuria with the use of SGLT2 inhibitors in diabetic patients with CKD Stage 3B or 4 which was not related to the change in HbA1c.[52] Another study based on a

TABLE 1 Risk of end-stage kidney disease associated with sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs.

Author, year	Location	Study design	Study population	Comparator	Duration of follow-up	Risk of kidney failure SGLT2 inhibitor vs. comparator, HR/OR (95% CI)
Heerspink et al., 2020[14]	Israel, Italy, Japan, Taiwan, and the UK	Observational cohort study	T2D patients, $n = 65\ 231$ Mean eGFR: 91 mL/min per 1·73 m^2	Other glucose-lowering drugs	14.9 months (mean)	HR: 0.33 (0.16–0.68)
Idris et al., 2022[47]	UK	Retrospective cohort study	T2D patients, $n = 46\ 876$ CKD prevalence in each group: 6.3% and 7.6%	DPP-4 inhibitors	2.1 years (median)	HR: 0.37 (0.25–0.55)
Nagasu et al., 2021[51]	Japan	Multicentre, real-world electronic health record-based registry	T2D patients with DKD, $n = 2066$ eGFR < 60 mL/min in each group: 26%–27% Proteinuria: 27%–28%	Other glucose-lowering drugs	21.0 ± 9.8 months	HR: 0.26 (0.11–0.61)
Koh et al., 2021[48]	Korea	Retrospective cohort study	T2D patients, $n = 90\ 032$ CKD prevalence in each group: 7.2% and 8.0%	Other glucose-lowering drugs	1.4 years (median)	HR: 0.47 (0.34–0.65)
Lin et al., 2021[49]	Taiwan	Retrospective cohort study	T2D patients, $n = 27\ 332$ CKD prevalence in each group: 40.6% and 40.9%	Oral glucose-lowering drugs	SGLT2 inhibitor: 9.2 months (mean) Oral glucose-lowering drugs: 8.1 months (mean)	HR: 0.42 (0.33–0.54)[a]
Xie et al., 2020[50]	USA	Retrospective cohort study	T2D patients, $n = 216\ 558$ Mean eGFR: 75 mL/min/1.73m^2	SUs DPP-4 inhibitors	SGLT2 inhibitor: 360 days (median) DPP-4 inhibitors: 535 days (median) SUs: 617 days (median)	Vs. SUs: HR: 0.55 (0.46–0.67) Vs. DPP4-inhibitors: HR: 0.62 (0.51–0.75)
Chan et al., 2023[55]	China	Retrospective cohort study	T2D patients with CKD Stage 3B-5, $n = 5800$	Other glucose-lowering drugs	12 months for all patients	OR: 0.48 (0.33–0.71)[#]
Htoo et al., 2024[32]	USA	Retrospective cohort study	T2D patients who initiated empagliflozin or cardioprotective GLP-1RA from 2014 to 2019. Propensity-score-matched pairs: 10837 with CKD stage 3–4	GLP-1 RA initiators	5 months (median)	HR: 0.75 (0.60–0.94)
Htoo et al., 2024[57]	USA	Retrospective cohort study	T2D patients who initiated empagliflozin or DPP-4 inhibitors from 2014 to 2019. Propensity-score-matched pairs: 8072 with CKD Stage 3–4	DPP-4 inhibitor initiators	5 months (median)	HR: 0.45 (0.35–0.58)

Note: HR corresponds to the risk of ESKD except for [#]renal outcome defined as a composite of doubling serum creatinine, sustained reduction in eGFR by >40%, ESKD or death from kidney-related causes.
Abbreviations: CI, confidence interval; CKD, chronic kidney disease; DKD, diabetic kidney disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio; OR, odds ratio; SGLT2, sodium-glucose cotransporter-2; SU, sulphonylurea.
[a]Sustained reduction in eGFR by >50%.

Japanese registry showed a significant decline in UACR for diabetic patients with CKD treated with an SGLT2 inhibitor for a median period of 13 months.[53] The DARWIN-TED study, conducted in 46 Italian outpatient clinics, showed a 37% reduction in albuminuria in patients treated with dapagliflozin versus those treated with other oral antidiabetic drugs.[54] A meta-analysis of observational studies showed a reduced risk of kidney failure with SGLT2 inhibitors in a real-world type 2 diabetes population when compared with other glucose-lowering drugs (HR 0.54, 95% CI 0.47–0.63).[45] This renoprotective effect of SGLT2 inhibitor treatment was also observed in individuals with CKD at baseline (HR 0.49, 95% CI 0.33–0.72).

In a population-based propensity-score-matched cohort study in Hong Kong, SGLT2 inhibitor use was significantly associated with lower rates of kidney-related events and MACE in patients with advanced DKD (mean eGFR 35.7 mL/min/1.73 m^2).[55] SGLT2 inhibitor users had a significantly lower rate of MACE (9.6% vs. 15.1%; $p < 0.001$), which was predominantly driven by a lower occurrence of heart failure hospitalization. There was also a lower rate of cerebrovascular events in SGLT2 inhibitor users.[55] SGLT2 inhibitors also resulted in a lower rate of MACE in the subgroup with a baseline eGFR below 30 mL/min/1.73 m^2.

In the large CVD-REAL-3 study, patients with type 2 diabetes who were initiating an SGLT2 inhibitor had a significant reduction in eGFR decline as compared to those receiving other glucose-lowering drugs during a mean follow-up of 14.9 months (difference in slope for SGLT2 inhibitors vs. other antidiabetic drugs of 1.53 mL/min/1.73 m^2, 95% CI 1.34–1.72; $p < 0.0001$ [Table 1]).[5] In that study, patients treated with SGLT2 inhibitors had a significantly lower rate of the composite kidney outcome (50% eGFR decline or occurrence of kidney failure). These results were consistent across countries and prespecified subgroups.[5]

The EMPRISE study is a large observational cohort based on electronic healthcare databases, designed to compare the safety and effectiveness of empagliflozin therapy with dipeptidyl peptidase-4 (DPP-4) inhibitor and GLP-1RA therapy, with a cardiovascular composite being the primary outcome and kidney failure being a secondary outcome. Results showed that the risk of kidney failure was significantly reduced with empagliflozin treatment compared with DPP-4 inhibitor treatment (HR 0.43, 95% CI 0.30–0.63) in adults with type 2 diabetes.[56] It should be noted that baseline eGFR was approximately 80 mL/min/1.73 m^2 in that analysis. Data obtained from the EMPRISE study focusing on the restricted subgroup of patients with a history of baseline CKD Stages 3–4 showed that empagliflozin initiation was associated with a lower risk of ESKD, as compared with propensity-score matching with those who initiated a DPP-4 inhibitor (HR 0.45, 95% CI 0.35–0.58 [Table 1]).[57] A similar protective propensity-score matching pattern with respect to the risk of ESKD was observed in the EMPRISE cohort when empagliflozin initiation was compared with GLP-1RA initiation (HR 0.75, 95% CI 0.60–0.94 [Table 1]).[32]

In addition, a large observational retrospective cohort study with 90 094 propensity-score-matched T2D patients over the age of 66 years reported a significantly lower risk of acute kidney injury events in SGLT2 inhibitor users as compared to GLP-1RA users (HR 0.85, 95% CI 0.79–0.92).[58] This is in agreement with other real-world evidence consistently showing a protective effect of SGLT2 inhibitors on the risk of acute kidney injury events.[59]

11 | EFFECTIVENESS OF SGLT2 INHIBITORS AMONG PATIENTS WITHOUT ALBUMINURIA

The absence of albuminuria in patients with chronic renal disease is not exceptional.[60] This can be explained by the predominance of fibrous tubulointerstitial lesions, by the presence of vascular lesions and also by the disappearance or masking of albuminuria under RAS blockade. It has been observed that even in patients with diabetes and without albuminuria, a decline of GFR of > 3 mL/min 1.73 m^2 may be observed in 20% of the individuals.[61] A small recent study examined whether SGLT2 inhibitors slowed the loss of GFR in patients with DKD without albuminuria. The authors showed that the mean annual change of eGFR in those treated with SGLT2 inhibitors in addition to RAS blockade was significantly lower than that in the control group (-1.15 ± 0.30 vs. -2.18 ± 0.30 mL/min/1.73 m^2/year [$p = 0.0173$]).[23] These results, albeit observed in a limited number of patients, suggest that SGLT2 inhibitor use in combination with RAS blockade may have a beneficial effect on decline in GFR even in the absence of albuminuria. This is in agreement with a post hoc analysis of the interventional DAPA-CKD trial, which a showed similar improvement in renal outcomes for those with the lowest urinary albumin excretion rate at baseline.[62] Results from a recent meta-analysis of observational studies reported a lower risk of kidney failure with SGLT2 inhibitors compared to other glucose-lowering drugs in diabetic people without albuminuria at baseline (UACR <3 mg/mmol: HR 0.61, 95% CI 0.52–0.71; UACR: 3–30 mg/mmol: HR 0.73, 95% CI 0.67–0.79).[45]

The OPTIMIZE-CKD study assessed the real-world effectiveness of dapagliflozin in patients with CKD and UACR < 200 mg/g in Japan and the United States, showing that dapagliflozin initiation was associated with a clinically meaningful attenuation of the eGFR slope.[63] These investigators assessed the effect of initiating versus not initiating dapagliflozin 10 mg on kidney function decline in patients with UACR < 200 mg/g by matching dapagliflozin initiators in a 1:1 ratio to a potential comparator patient had not initiated treatment on the same date and had the closest matching propensity score. Up to five potential comparators were randomly sampled for each dapagliflozin initiator in chronological order of their index dates and matched based on age, sex, heart failure diagnosis, T2D diagnosis, and RAS inhibitor prescription. The primary outcome was eGFR slope between index date and the end of follow-up. In total, 20 407 dapagliflozin initiators were included in the analysis, with a median age of 73 years (United States), 77 years (Japan, Real World Data database) and 71 years (Japan, Medical Data Vision database). Investigators noted that dapagliflozin 10 mg was initiated in patients across all CKD stages, but mostly in those with CKD Stage 3–4 (69%–81% across

databases). Following dapagliflozin initiation, the difference in median eGFR slope between initiators and matched non-initiators was significant (1.07 mL/min/1.73 m^2/year; 95% CI 0.40–1.74) in all patients with UACR < 200 mg/g. Of note, the benefit of dapagliflozin 10 mg initiation was observed across the entire eGFR slope distribution among patients with UACR < 200 mg/g.[63]

12 | LOWER RISK OF HYPERKALAEMIA WITH SGLT2 INHIBITOR USE

In a large population-based cohort in the United States, the risk of hyperkalaemia after initiation of SGLT2 inhibitors was lower versus DPP-4 inhibitors in patients with T2D and CKD Stages 3–4 (adjusted HR 0.74, 95% CI 0.68–0.80). After propensity-score matching, hyperkalaemia risk was also reduced after initiation of GLP-1RAs versus DPP-4 inhibitors (adjusted HR 0.80, 95% CI 0.75–0.86).[64] There was a lower risk of hyperkalaemia for SGLT2 inhibitors versus GLP-1RAs (adjusted HR 0.92, 95% CI 0.86–0.99). Similar results were observed when the outcome studied was hyperkalaemia diagnosis in the inpatient or emergency department setting, with HRs of 0.76 (95% CI 0.58–0.99) for SGLT2 inhibitors versus DPP-4 inhibitors and 0.66 (95% CI 0.54–0.80) for GLP-1RAs versus DPP-4 inhibitors.[64] The authors found consistent results across subgroups, in particular for those with a history of heart failure and CVD and for those on medications that influence serum potassium levels. These results are in agreement with findings from an RCT confirming that, in patients with diabetes and CKD, SGLT2 inhibitors significantly reduced the risk of severe hyperkalaemia without increasing the risk of hypokalaemia.[65]

13 | RISK FACTORS FOR THE INITIAL eGFR CHANGE AND KIDNEY OUTCOMES WITH SGLT2 INHIBITORS

Initiation of the treatment with SGLT2 inhibitors is associated with an initial decline in eGFR of approximately 3 to 6 mL/min/1.73 m^2, which is followed by a stabilization of the downward slope, thereby conferring a long-term nephroprotective effect. A recent study analysed the impact of different therapeutic classes often prescribed in association with SGLT2 inhibitors on the early decrease in eGFR and long-term kidney outcomes. The authors used a large database from a Taiwanese health register, including 10 071 patients who had received SGLT2 inhibitor treatment. Direct comparisons of eGFR trajectory over time were made according to the concomitant use of background medication. A propensity-score matching analysis was used to compare each group of patients receiving a SGLT2 inhibitor according to the baseline characteristics.

The authors showed that there were no differences in either the impact on the early decline in eGFR or the evolution of the eGFR slope over the long term between dapagliflozin and empagliflozin or for the comparison between low and high doses of SGLT2 inhibitors.[55]

The authors reported 246 (2%) events of an abrupt decline of >30% in eGFR within 12 weeks for the 10 071 patients after SGLT2 inhibitor treatment. The results of propensity-score matching pair analysis indicated that, compared with the use of no drugs, the use of thiazide diuretics, loop diuretics, insulin, and fenofibrate was associated with a higher risk of abrupt eGFR decline, whereas metformin treatment was associated with a lower risk of initial eGFR decline of >30%.[55]

Use of an RAS inhibitor was associated with an attenuated eGFR decline 24 weeks after SGLT2 inhibitor treatment compared with no use of an RAS inhibitor (−0.38 [0.44] vs. −1.72 [0.43] mL/min per 1.73 m^2/year; $p = 0.028$).[55] In contrast, the use of loop diuretics was associated with worse composite kidney outcomes (HR 1.88, 95% CI 1.19–2.96) compared with no drug use during the follow-up period.[55] In summary, these data based on a large population showed that treatment with diuretics and fenofibrate increased the risk of a significant initial decline in GFR. Over the long term, treatment with RAS blockers was more nephroprotective. Diuretics, probably by inducing a greater haemoconcentration, increased the risk of kidney outcomes over the long term. However, this was a retrospective study and comparison using a propensity score has some limitations. It is possible that patients treated with loop diuretics had more severe cardiorenal disease, including advanced heart failure. Nevertheless, these results highlight the importance of combining RAS blockade with the prescription of an SGLT2 inhibitor for long-term nephroprotection and emphasize that diuretic treatment increases the risk of a significant decline in eGFR over the first few weeks of treatment after SGLT2 inhibitor initiation.

14 | CONCLUSION

Chronic kidney disease is associated with substantial morbidity, mortality and costs. Real-life assessments in various countries have shown that adherence to guideline implementation remains poor among patients with DKD. In parallel, real-world evidence studies suggest that the attainment of multiple treatment targets is associated with an improved cardiorenal prognosis in patients with DKD, thus supporting the recommendation of comprehensive care targeting multiple criteria such as BP, albuminuria, glycaemia, RAS blockade and SGLT2 inhibition.

Real-world evidence provides complementary insights to those obtained from RCTs, with real- world data confirming the effectiveness of renoprotective drugs such as SGLT2 inhibitors, GLP-1RAs and MRAs with regard to the risk of kidney failure. These findings contribute to extending the applicability of these treatments in routine clinical practice.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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