Received: 21 March 2019 | Revised: 11 April 2019 | Accepted: 22 April 2019

DOI: 10.1002/edm2.72

REVIEW ARTICLE

Endocrinology, Diabetes & Metabolism Open Access WILEY

Safety and efficacy of antihyperglycaemic agents in diabetic kidney disease

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Funding information
NIH, Grant/Award Number: R01DK117599, R01DK104753, R01CA227493, U54DK083912, UM1DK100846, U01DK116101 and UL1TR000460; Hoffman-La Roche; Boehringer Ingelheim

Abstract

Diabetic kidney disease (DKD) is the major contributor to the mortality and the financial burden of diabetes, accounting for approximately 50% of the cases of end-stage renal disease (ESRD) in the developed world. Several studies have already demonstrated that achieving blood pressure targets in DKD with agents blocking the renin-angiotensin system confer superior renoprotection when compared to other agents. However, the effects on renal outcomes of antihyperglycaemic agents in these patients have not been reported or studied broadly until recent years. The intent of this article is to review the available data on safety, efficacy, impact on renal outcomes and pathophysiology implications of the most utilized antihyperglycaemic agents in DKD/ESRD.

KEYWORDS

antihyperglycaemic agent, chronic kidney disease, diabetic kidney disease, efficacy, safety

1 | EPIDEMIOLOGY OF DIABETES AND DIABETIC KIDNEY DISEASE

Diabetes mellitus represents one of the major epidemic concerns and hazard to global human health, since its incidence and prevalence have continued to increase in the past decades. The International Diabetic Federation (IDF) recently published that in 2017 there were 425 million people worldwide with diabetes, with a projected rise to 629 million by 2045.[1] In the United States, it is estimated that 30.3 million people of all ages suffered from diabetes in 2015, representing 9.4% of the US population according to the 2017 National Diabetes Statistics Report.[2] Among different macrovascular and microvascular complications of diabetes, diabetic nephropathy or more broadly diabetic kidney disease (DKD) is defined by the presence of albuminuria (urinary albumin to creatinine ratio more than 30 mg/g) in two separate occasions three-month apart and/or sustained reduction in eGFR below 60 mL/min/1.73 m^2 and/or histological evidence of DKD on a kidney biopsy. DKD is the most common cause of ESRD and represents a strong independent risk factor for cardiovascular morbidity and mortality in patients with diabetes.[3,4] Despite this, early diagnosis and management of DKD has remained inefficient, resulting in a rise to up to 94% in the number of deaths from the year 1990 to 2012 attributed to DKD, showing that prevention of DKD development and progression remains vastly unsuccessful.[5]

Sebastian Niezen and Humberto Diaz del Castillo are co-first authors.

2 | RELEVANCE OF HBA1C TARGET FOR DKD DEVELOPMENT AND PROGRESSION

Progression of DKD to ESRD can be delayed if glycaemic control is optimal with glycosylated haemoglobin (HbA1c) targets around 7.0%, as recommended by the American Diabetes Association (ADA).[6] The beneficial effects of targeting HbA1c on DKD onset has been undisputedly proven throughout several studies and trials including the Diabetes Control and Complications Trial, the United Kingdom Prospective Diabetes Study, the Veterans Affairs Diabetes Trial and the Steno-2 Study, which all reported a correlation between achieved HbA1c targets and reduction of diabetic microvascular complications (diabetic retinopathy, neuropathy, and nephropathy).[7-10] The inquiry of whether intensifying glycaemic control would provide additional benefits to microvascular and macrovascular events was assessed in the ACCORD and the ADVANCE trials. In the ACCORD trial, which recruited more than 10 thousand patients a third of which had prior cardiovascular events, the intensive therapy group targeting a HbA1c < 6% showed an increased rate of death of any cause (5.0% vs 4.0%; hazard ratio, 1.22; 95% CI: 1.01-1.46; $P = 0.04$) and increased mortality from cardiovascular causes (2.6% vs 1.8%; hazard ratio, 1.35; 95% CI: 1.04-1.76; $P = 0.02$) when compared with the standard therapy group aiming for HbA1c of 7.5%. The ADVANCE trial compared the effect of achieving a HbA1c target of 6.53%-7.29%: even though a significant reduction in renal events including new or worsening albuminuria was observed, this study also showed no evidence of reduction of major macrovascular events and rates of death.[11] Overall, these data suggest that caution should be taken when trying to achieve HbA1c targets below 7%, at least in patients with prior cardiovascular events. These studies also raised the question of what the HbA1c target should be in advanced CKD and ESRD patients. In fact, the mortality risk curve in maintenance dialysis patients clearly demonstrates a J shape, with ideal targets between 7% and 9%.[12] In fact, several studies have shown that HbA1c targets <6.5% and > 9% are associated with an increased risk for all causes mortality and macrovascular events in both patients with CKD and ESRD, concluding that HbA1c less than 7% should be avoided in chronic haemodialysis patients.[13-16]

3 | ACCURACY OF HBA1C DETERMINATION IN ADVANCED CKD AND ESRD

For patients that reach advanced DKD and ESRD, the accuracy of HbA1c measurements has been controversial. Many elements can contribute to falsely decreased reported levels of HbA1c, including the reduction of red blood cell lifespan, anaemia, malnutrition, blood transfusions, blood pH levels, iron supplementation and supplemental treatment with recombinant humanized erythropoietin, which are all often present in advanced DKD.[17] As a result, other markers of glycaemic control for patients in dialysis treatment have been suggested and some are currently under study, such as glycated albumin, glycosylated fructosamine, 1,5-anhydroglucitol and continuous glucose monitoring.[17] In several studies, glycated albumin has proved better association with macrovascular and microvascular disease as compared to HbA1c, and an even improved correlation with glycaemic status in patients with haemodialysis or peritoneal dialysis. On the other hand, fructosamine has proven to be as reliable as HbA1c in patients with haemodialysis and has been described as an accurate measurement in patients with controlled glucose levels. Finally, 1-5 anhydroglucitol has been proven to be an effective marker for diabetes risk and complications in patients that are not in CKD stages above 3, since its reabsorption is altered. Nonetheless, all of these markers are still under study and require more evidence to determine the precise stages or window in which they can be either more or as accurate than HbA1c.[17]

Although the ideal HbA1c target in CKD is still not well defined and the reliance of HbA1c measurements in these patients is questionable, current KDOQI Clinical Practice Guidelines for Diabetes and CKD recommendations are to maintain a value around but not less than 7.0%.[3] This is extremely important, since these patients are at high risk of hypoglycaemia as a consequence of their deficient renal drug clearance, insulin degradation and impaired gluconeogenesis.[3]

4 | CHOICE OF ANTIHYPERGLYCAEMIC AGENTS IN DKD

In general, treatment of type 2 diabetes mellitus (T2DM) initially consists of lifestyle modifications and monotherapy with an antihyperglycaemic agent.[18,19] While a large inter-individual variability has been described in HbA1c targets achieved with lifestyle changes, on average monotherapy of any antihyperglycaemic agent can decrease HbA1c levels by approximately 1% (range of 0.6%-1.5%), irrespectively of specific pharmacodynamics or pharmacokinetics profiles.[20] According to the American College of Physicians (ACP), the American Diabetes Association (ADA), and the American Association of Clinical Endocrinologists (AACE), the choice of therapy should be made based on glycaemic efficacy, safety profiles, effects on weight, hypoglycaemic risk, comorbidities of the patient, routes of administration, patient preference and cost. Even though these variants may influence therapeutic decisions, the general consensus favours metformin as initial agent for monotherapy.[21] According to the ADA guidelines, pharmacologic monotherapy should start at the value of HbA1c above 7%, adding a second agent after 3 months if goal is not reached. Initial dual therapy should be considered in patients with HbA1c above 9% in newly diagnosed T2DM.[22] As second-line agents, ADA and AACE differ in the optimal options, where ADA is more inclined on the use of sulfonylureas, thiazolidinediones, DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 agonists or basal insulin.[23] Despite the fact that these agents are all effective in lowering HbA1c levels, their unique and individual effect on renal outcomes as well as their safety profile in patients with different stages of DKD has generated a lot of interest.[24] As many new agents have come

on the market in the past few years, we will now review the safety and the HbA1c-independent beneficial effects on renal endpoints of different antihyperglycaemic agents. For each class of drugs, we will summarize the experimental data supporting specific renoprotective mechanism of each agent.

5 | INSULIN SENSITIZERS

When looking at both patients with T1DM and T2DM, it is clear that insulin resistance correlates with and predicts albuminuria, suggesting a causative role of altered insulin receptor signalling in the pathogenesis of DKD.[25] Interestingly, insulin sensitizers of the class of thiazolidinediones have also suggested an additional renoprotective effect reducing albuminuria when compared to standard of care (even when achieving the same HbA1c targets).[26] More recently, the REMOVAL trial, although not designed to look at eGFR as primary outcome, suggested that addition of metformin in patients with T1DM already treated with insulin may confer a beneficial effect on the loss of eGFR observed at 36 months.[27]

If and how insulin sensitizers may directly protect the kidney has been investigated in the past few years. Among several cells of the glomerular filtration barrier, podocytes express all the elements of the insulin signalling cascade, and we and others have shown that glomerular and podocyte insulin resistance is already present at time of albuminuria onset.[28-30]

The mechanism by which altered insulin signalling may contribute to DKD remains unknown. While multiple pathways may be involved,[31,32] we have clearly demonstrated that impaired lipid metabolism in glomerular cells is a key mediator of cellular insulin sensitivity and susceptibility to injury in DKD, as pharmacological reduction of cholesterol in podocytes is sufficient to prevent from the development of DKD and to restore insulin signalling.[33] Considerations about each specific insulin sensitizer are provided below.

5.1 | Metformin

Metformin hydrochloride is the preferred initial pharmacological agent used in all T2DM patients that failed lifestyle modifications recommended by the ADA guidelines and the European Association of Study of Diabetes if no contraindication is present. It is the favoured agent due to low cost, effectiveness, neutral impact on body weight and tolerability with minimal risk of hypoglycaemia.[34] Metformin reduces glycaemia primarily by inhibiting hepatic glucose production and enhancing insulin sensitivity in peripheral tissues; resulting in decreased endogenous glucose production and increasing glucose uptake.[35] Aside from its effect on glucose, metformin produces a pleiotropic effect through inhibition of the respiratory-chain complex 1 of the electron transport chain in the mitochondria through AMP-activated kinase (AMPK), known to regulate cellular metabolism, reducing the production of reactive oxygen species (ROS).[35]

The drug's efficacy lowering haemoglobin HbA1c at the different available doses ranges from 0.9% to 2.0% reduction, at 500 mg/daily and 2000 mg/daily, respectively, with no hypoglycaemic events when used as monotherapy. Most common side effect is gastrointestinal intolerance such as diarrhoea.[36] A major concern is metformin-associated lactic acidosis, usually seen in advanced DKD (eGFR <30 mL/min/1.73 m^2) or acute kidney failure leading to metformin accumulation resulting in type B lactic acidosis possibly due to mitochondrial dysfunction.[37] Although there is not enough evidence to ensure lactic acidosis is caused solely by metformin, restrictions in terms of dosage and use should be enforced in order to avoid possible toxicity caused by impaired renal clearance. By the ADA and US FDA, metformin is contraindicated in patients with an eGFR <30 mL/min/1.73 m^2, and it is recommended to avoid starting metformin in patients with a eGFR between 30 and 45 mL/min/1.73 m^2.[38] This is an important improvement when compared to prior recommendations that were more restricted and based on serum creatinine, even more in light of the potential renoprotective effect of metformin suggested by the REMOVAL trial, which indicate significant preservation of eGFR at 36 months.[27] Mechanistically, the potential renoprotective effect of metformin has been linked with activation of the inhibitory effect mentioned previously in mitochondrial respiratory chain and reducing oxidative stress.[39,40] Additional favourable effects include its weight neutrality by increasing satiation with potential weight loss effect, along with improvement in lipid profile,[38] which can both contribute to confer further renoprotection.

5.2 | Thiazolidinediones (TZDs)

TZDs are a group of antihyperglycaemic drugs that work by increasing insulin sensitivity in peripheral tissues, liver and adipose tissues potentiating insulin effect by acting as ligand of peroxisome-proliferator-activated receptors gamma (PPARγ), a nuclear receptor superfamily that regulates gene expression.[41] This group of agents are considered as second-line option or add-on treatment according to the ADA.[42] TZDs' efficacy in HbA1c reduction ranges from 1.0% to 1.5%.[43] Additionally to HbA1c reduction, TZDs may have a potential benefit preserving renal function in early stages of DKD and decreasing progression of albuminuria.[44,45] These ameliorating effects in DKD are considered to be independent of the achieved HbA1c and are thought to be secondary to decrease in oxidative stress and inflammation.[46]

An advantage of TDZ drugs is that no dose adjustment is needed in the presence of advanced CKD or haemodialysis. Nevertheless, TZDs are associated with body weight gain (4.9 kg ± 4.5 kg, $P < 0.01$), extracellular fluid increase (1.2 L ± 0.2 L, $P < 0.01$) and increased incidence of heart failure (RR 1.33, 95% CI: 1.14-1.54).[47,48] Because of this effect, they are contraindicated in New York Heart Association heart failure classes III and IV and cautious consideration with dose adjustment should be made in patients with mild heart failure.[49]

6 | INSULIN SECRETAGOGUES

6.1 | Sulfonylureas

Sulfonylureas (SUs) were the first oral agents to treat T2DM and have been used for over 60 years. SUs work by stimulating the β-cells in the pancreas to increase insulin secretion and decreasing hepatic insulin clearance independently of hyperglycaemia.[50] SUs are recommended to be used after and in combination with metformin as dual therapy and frequently used due to low cost and high effectiveness. Several studies have proven that SUs reduce HbA1C from 1.0% to 2.0% on average as monotherapy and combination, respectively.[51]

SUs have a higher risk of hypoglycaemia in comparison with other oral antihyperglycaemic drugs and should be cautiously dosed in patients with DKD.[3] Since most SUs are eliminated by the kidneys, dose adjustment or drug discontinuation should be considered in advanced DKD stages.[3] Considering these facts, glipizide is the preferred 2nd generation SU as no dose adjustment is needed on moderate to severe CKD with no increased risk of hypoglycaemia. Another commonly utilized agent, glyburide, should be avoided in CKD stages 3-5, while glimepiride can be used in CKD stage 3 with caution (Table 1).[52]

No evidence of renoprotective effects such as decreasing albuminuria or delaying DKD progression has been recognized as attributable to SUs.[53] The reports to be exposed in June 2019 of the CAROLINA trial will provide evidence of long-term outcomes of glimepiride vs linagliptin considering cardiovascular as primary and renal as secondary endpoints.[54]

6.2 | GLP-1 RAs

Glucagon-like peptide 1 (GLP-1) receptor agonists (RA) are drugs classified as incretin-based therapies. The main incretins in humans are GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), which are secreted by the intestines after every meal. GLP-1

TABLE 1 Safety of different antihyperglycaemic agents at different stages of eGFR

eGFR (mL/min/1.73 m^2)	<15	15-30	30-45	45-60	>60
Biguanides					
Metformin	No	No	No.	Yes	Yes
Thiazolidinediones					
Rosiglitazone	Caution	Caution	Yes	Yes	Yes
Pioglitazone	Caution	Caution	Yes	Yes	Yes
SUs					
Glipizide	Yes	Yes	Yes	Yes	Yes
Glyburide	No	No	No	No	Yes
Glimepiride	No	No	Adjust	Adjust	Yes
GLP-1 RA					
Liraglutide	Yes	Yes	Yes	Yes	Yes
Exenatide	No	No	Yes	Yes	Yes
Lixisenatide	No	No	Yes	Yes	Yes
Albiglutide	No	Caution	Yes	Yes	Yes
DPP-4 Inhibitors					
Linagliptin	Yes	Yes	Yes	Yes	Yes
Sitagliptin	Adjust	Adjust	Yes	Yes	Yes
Saxagliptin	Adjust	Adjust	Adjust	Adjust	Yes
Alogliptin	Adjust	Adjust	Adjust	Adjust	Yes
Meglitinides					
Repaglinide	Caution	Caution	Yes	Yes	Yes
Nateglinide	Caution	Caution	Yes	Yes	Yes
SGLT-2 Inhibitors					
Canagliflozin	No	No	No	Yes	Yes
Dapagliflozin	No	No	No	No	Yes
Empagliflozin	No	No	No	Yes	Yes
Ertugliflozin	No	No	No	No	Yes
Insulins	Insulin dose should be reduced by 25% when it reaches eGFR between 10 and 50 mL/min, and up to 50% when it is below 10 mL/min.				

receptor agonists then, work by the stimulation of GLP-1 receptors, enhancing insulin secretion, appetite suppression, delaying gastric emptying, and inhibiting glucagon release from the pancreas.[55] Current clinically used GLP-1 RAs are resistant to Dipeptidyl Peptidase 4 (DPP4) cleavage and are generally long-acting drugs, reducing HbA1C with a variability between 1.3% and 1.9%.[56] GLP-1-RAs use has increased in the past decade due to their efficacy and mostly due the low risk for hypoglycaemia and their beneficial effect on weight loss.[57]

Besides their glucose-lowering effects, some GLP-1-RAs show benefit in cardiovascular outcomes (CVOT). In the LEADER trial, liraglutide showed superiority with less CV events when compared to placebo.[58] A second analysis of LEADER trial, focusing on renal outcomes, showed liraglutide had fewer overall composite renal outcomes (persistent doubling of serum creatinine, persistent macroalbuminuria, ESRD and death caused by renal disease) when compared to placebo. Nevertheless, doubling of serum creatinine, ESRD and death from renal disease were not significantly altered. Therefore, the major effect of liraglutide resides in a reduction of new onset of macroalbuminuria, with fewer events occurring in the liraglutide group vs placebo (HR 0.74, 95%, 0.60 to 0.91; $P = 0.004$). It is also interesting to note that a subgroup of patients with a eGFR 30-59 mL/min/1.73 m^2 receiving liraglutide over 36 month showed a decrease in GFR of 2 mL/min/1.73 m^2 vs 4 mL/min/1.73 m^2 seen in placebo.[59]

Similarly, in the AWARD-7 trial, dulaglutide showed a considerable decrease in albuminuria and delay in eGFR decline in patients with advanced DKD (stage 3-4) in comparison with patients receiving insulin glargine.[60] The SUSTAIN 6 trial involving semaglutide reported as a secondary outcome lower risk of new or worsening macroalbuminuria against placebo (HR 0.64 CI 95% 0.44-0.88), and showed superiority against placebo in primary CVOT.[61] Furthermore, the ELIXA trial evaluating lixisenatide in acute coronary syndrome showed no inferiority in CVOT, but reported lower albuminuria with treatment vs placebo.[62] For exenatide, the EXSCEL trial did not evaluate or report the effects on urinary albumin-creatinine ratio (UACR) or GFR. In summary, both liraglutide and dulaglutide displayed a potential renal benefit in the preservation of eGFR and a substantial decrease in albuminuria independently of improvement of glycaemic control, while semaglutide only showed lower risk of albuminuria. The mechanism might involve a direct effect of GLP-1 in the kidneys decreasing oxidative stress, inflammation and accumulation of collagen.[63]

Safety of most GLP-1 RAs in patients with CKD has not been clearly evaluated, and therefore, excluding liraglutide, their use is not recommended in patients with eGFR < 30 mL/min/1.73 m^2.[64,65] In terms of general adverse events, nausea, vomiting and diarrhoea are the most frequently reported and as such they can predispose to prerenal acute kidney injury. Nonetheless, a direct effect of GLP-1 RAs in protecting from kidney damage has not been established but is suggested by the evidence that GLP-1 RAs are highly expressed in the kidney.[66,67]

6.3 | Dipeptidyl peptidase 4 (DPP-4) inhibitors

In response to a meal, the half-life of GLP-1 is <2 minutes as it is quickly degraded by the DPP4 membrane glycoprotein, a well-known catalytic protein with affinity to incretins as well as other substrates.[68] Therefore DPP-4 inhibitors were developed as novel oral glycaemic agents since they prolong GLP-1 half-life by modulating postprandial glucose, fasting blood glucose and ultimately decreasing HbA1C. DPP-4 inhibitors should be considered either as an alternative add-on in dual or triple therapy or as an alternative monotherapy treatment when metformin is contraindicated.[22]

Current FDA-approved DPP-4 inhibitors include sitagliptin, saxagliptin, alogliptin, linagliptin with a clinical efficacy in HbA1c reduction of 0.5% as monotherapy and increased effectiveness when used as dual therapy.[69] Aside from their efficacy, DPP-4 inhibitors exhibit multiple advantages when treating patients with T2DM. These include a favourable tolerability with low risk for hypoglycaemia in individuals with advanced CKD, a neutral weight gain and an ability to reduce albuminuria.[69]

In terms of renal effects, data from the cardiovascular outcomes trial SAVOR-TIMI 53 for saxagliptin showed a significant mean reduction in patients with urinary albumin/creatinine ratios (UACR) of −34 mg/g compared to placebo after 2 years of treatment, mainly driven in individuals with UACR > 300 mg/g at baseline. Similar findings were observed in all ACR categories. Furthermore, even after stratifying by baseline eGFR, saxagliptin treatment was associated with a decrease in albuminuria in all categories after 2 years, with −19.3 mg/g for GFR > 50 mL/min/1.73 m^2, −105 mg/g for GFR 30-50 mL/min/1.73 m^2 and −245.2 mg/g for eGFR < 30 mL/min/1.73 m^2. While no meaningful effect in the preservation of eGFR between treatment group and placebo was observed, potential renoprotective effects in long-term renal outcomes studies are yet to be determined.[70] Although the association between ACR levels and increased CV risk has been demonstrated previously, the potential beneficial relationship between the ACR reduction seen in this trail and its effect in CV risk in these patients was not determined.[70]

For another commonly utilized agent, 360 patients with T2D, eGFR equal or above 30 mL/min/1.73 m^2 and UACR between 30 and 3000 mg/g were randomized to either receive linagliptin or placebo for 24 weeks in the MARLINA-T2D study.[71] At the end of the study, HbA1c below 7.0% was achieved by more individuals in the linagliptin group that in placebo: 36.2% compared to 9.3%, although the percentage change in UACR between these two had only a difference of 0.9%, proving to have an insignificant lowering effect in albuminuria, at least in the time frame of the study.[71] In the TECOS trial, which evaluated cardiovascular outcomes with sitagliptin, renal outcomes for patient with CKD stages 1-3b were evaluated over 4-year follow-up. Sitagliptin did not show a significant impact in delaying CKD progression against placebo with a mean eGFR decline −4.0 vs 2.8 mL/min/1.73 m^2, respectively, with a nonsignificant UACR reductions against placebo over 4 years as well (−0.18 mg/g 95% CI: 0.32-0.02 $P = 0.032$). Additionally, sitagliptin was not superior to placebo in cardiovascular outcomes.[72]

Specifically for alogliptin, the EXAMINE trial demonstrated safety of alogliptin in terms of major adverse cardiac event in T2DM patients for a median of 17.5 months. Although the focus of the trial was not on renal outcomes, the overall safety profile of alogliptin was similar to placebo with no apparent differences in reduction of GFR, increase in blood creatinine, proteinuria and renal impairment (80% of general adverse events were reported in alogliptin vs 78.8% with placebo). [73]Another recent trial, CARMELINA, involved T2DM patients with high CV risk and kidney events including DKD. It analysed a total of 6979 patients randomized to either linagliptin or placebo for a median of 2.2 years. In this study, linagliptin treatment resulted in a less frequent progression of albuminuria than placebo (35.3% vs 38.5%) ($P < 0.03$). Sustained ESRD or death due to renal failure was not statistically different among groups (linagliptin 3.9% vs 4.4% placebo).[74] The ongoing phase 3 CAROLINA trial, which compares the effect of linagliptin to glimepiride on CV outcomes in T2DM, will shed further light on the efficacy of linagliptin on CV (primary) and renal (secondary) endpoints, which will be captured as transition in albuminuria classes.[74,75]

A significant reduction in albuminuria has also been observed in SAVOR-TIMI 53 trial and in smaller retrospective studies looking only at patients with macroalbuminuria (>300 mg/g).[75] Several mechanisms have been proposed, considering that DPP-4 is highly expressed in the kidneys and mostly in proximal tubule, glomerulus and endothelial cell. DPP-4 inhibitors have shown in experimental models to increase cAMP, resulting in reduction of reactive oxygen species and decreasing inflammation. Likewise, they have also proven to provide renoprotective effects via increasing GLP-1 levels, which exerts anti-inflammatory properties as previously discussed.[76,77] Overall, DDP-4 inhibitors are a good choice for patients with DKD; however, as all available DPP-4 inhibitors have distinctive metabolism and route of excretion, most of them would require different dose adjustments depending on eGFR (Table 1).[78]

6.4 | Meglitinides

The most utilized agents in this family, repaglinide and nateglinide, share the same mechanism of action as SUs, as they bind to the sulfonylurea receptor in the beta cells of the pancreas but in a rather weaker manner and different place than SUs, resulting in a shorter effect in relation with time.[79] In terms of efficacy, repaglinide has shown to be superior to nateglinide decreasing HbA1C (1.5% vs 1.0%) with lower incidence of hypoglycaemic events.[80] In terms of safety, studies have focused mainly on the potential of meglitinides of causing hypoglycaemic events, where patients with DKD can present a 1.9-fold greater risk of developing hypoglycaemia compared to meglitinide nonusers. Among these agents, specifically repaglinide has reported higher incidence of hypoglycaemia compared to nateglinide in patients with type 2 diabetes (17.2% vs 6.1%).[81-83] Based on these results, KDOQI guidelines recommend starting nateglinide and repaglinide in a conservative manner, with doses of 60 mg for nateglinide and 0.5 mg in repaglinide for patients in CKD stage 4-5.[3] Neither experimental nor clinical studies have yet been designed to assess whether there is a direct impact of these agents on renal outcomes.

7 | GLYCOSURICS

7.1 | SGLT-2 Inhibitors

Sodium glucose cotransporter-2 (SGLT2) inhibitors are the newest class of antihyperglycaemic drugs on the market, being first approved in 2013. These agents act on the sodium glucose cotransporter 2, which is in charge of reabsorbing glucose in the proximal tubular epithelial cells of the kidney. SGLT2 is located in the brush border of the S1 and S2 segments of the proximal tubule and it is in charge to reabsorb about 90% of glucose that is filtered through the glomerulus.[84] As a result, agents that inhibit this cotransporter specifically cause a decrease in the reabsorption of glucose in the proximal tubule and promote urinary glucose loss, creating a glucose-lowering effect that is independent of insulin.[85] Experimental studies strongly suggest that these agents may provide renoprotection through a hemodynamic mechanism that regulates tubuloglomerular feedback mediated by increase distal delivery of sodium, which in turn increase afferent arteriole tone reducing glomerular hyperfiltration. However, the possibility that SGLT-2 inhibitors may interfere with the metabolic function of tubular cells or may affect neoglucogenesis remains to be tested. Furthermore, the recent evidence that agents from this class can affect the function of the Na/H exchanger 1 (NHE-1) in cardiofibroblasts challenges their specificity and open the avenue for a different interpretation of their claimed mechanism of action.[86] Irrespectively of the mechanism responsible for renoprotection, further studies are also needed to understand the reported decreased urinary excretion of ketone bodies in some patients, predisposing them to ketoacidosis.[85,87,88]

Clinical studies focused on the efficacy of SGLT2 inhibitors have shown an average decrease in HbA1c of 0.5%-0.9%.[88-91] Adding SGLT2 inhibitors in patients receiving first-line monotherapy resulted in an increase proportion of subjects achieving a HbA1c <7%, with low risk of hypoglycaemic events.[90] In addition to glycaemic control, SGLT2 inhibitors cause a weight reduction of approximately 2 kg already at 6 weeks after initiation of therapy.[91,92] The most common adverse events include urinary tract infections and vulvovaginitis/balanitis with higher incidence in female than male, which could be linked to an increase urinary glucose excretion and which may limit utilization of this drug in immunocompromised patients.[93]

Efficacy of SGLT2 inhibitors is vastly dependent on GFR. Therefore, clinical studies and ADA guidelines state that these drugs should not be initiated in eGFR <60 mL/min/1.73 m^2 and should be stopped when eGFR < 45 mL/min/1.73 m^2.[94] In the Empagliflozin Cardiovascular Outcome Event Trial in T2DM patients (EMPA-REG Outcome), enrolled 7021 patients with eGFR above 30 mL/min/1.73 m^2 were randomized to empagliflozin or placebo daily. Incidence of new or worsening kidney disease

occurred with less frequency (12.7%) in the patients treated with empagliflozin than with placebo (18.8%; $P < 0.001$) with a relative risk reduction of 39%. More importantly, the EMPA-REG trial showed less amount of increased serum creatinine levels as well a reduced amount of initiation of replacement therapy in patients with empagliflozin vs placebo (1.5% vs 2.6% for doubling of serum creatinine levels and 1.5% vs 2.6% in renal replacement therapy initiation).[95,96] Aside from renal function protection, a very significant superiority on cardiovascular outcomes was observed in the treatment group vs placebo.[95,96]

On the other hand, the most recent Canagliflozin Cardiovascular Assessment Study trial (CANVAS) evaluated patients with T2DM to receive either canagliflozin or placebo. After a follow-up to 338 weeks, patients treated with canagliflozin demonstrated a regression of albuminuria (89.4 participants per 1000 patient-years vs 128.7 participants per 1000 patient-years ($P < 0.05$) and renal function preservation compared to placebo, suggesting and supporting a renoprotective effect in DKD.[97] Nonetheless, it is important to highlight the amputation rate increase in patients in treatment with canagliflozin compared to placebo as a secondary outcome as well, with 6.3 participants per 1000 patient-years vs 3.4 participants per 1000 patient-years ($P < 0.05$).[97] Nonetheless, this adverse effect still remains to be studied and proven, as it may simply reflect the higher probability of these patients to be accepted for surgery as they present a better preoperatory glycaemic control. Another ongoing trial for canagliflozin, named the Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy (CREDENCE) is expected to complete in 2019.[97,98] It aims to analyse the risk of canagliflozin vs placebo in terms of renal and cardiovascular outcomes in patients with established kidney disease, by enrolling 4401 adults with T2DM with eGFR between 30 and 90 mL/min/1.73 and albuminuria.[98,99]

Dapagliflozin has also been suggested to exert direct renoprotection. A randomized, double-blind, placebo-controlled study that included 252 patients with CKD stage 3A/B showed significant shifting to lower categories for albuminuria despite no significant difference in eGFR and HbA1c, strongly suggesting that renoprotection by SGLT2 inhibitors may strongly depend on eGFR.[100] Ongoing clinical trial evaluating the long-term effect of dapagliflozin on renal outcomes and cardiovascular mortality in patients with CKD (DAPA CKD) is expected completion in 2020. This trial is focused on the effect of this SGLT2-inhibitor compared to placebo on renal outcomes/mortality and cardiovascular mortality in patients with CKD, with an estimated enrolment of 4000 participants.[101] Aside from cardiovascular and renal protection, this class of agents is also associated with a reduction of systolic and diastolic blood pressure of −4.0 mm Hg and −1.6 mm Hg, respectively.[101,102]

Other trials for SGLT2-inhibitors either recently finished or which remain to be finished for 2019-2020 include DAPA-HF, DECLARE-TIMI58, VERTIS-CV, EMPEROR-Preserved, and EMPEROR-reduced, all of them mostly focusing on cardiovascular outcomes.[103]

8 | INSULIN

As a result of the progressive loss of beta cell function observed in T2DM, or of failure to properly control HbA1c on oral agents, a certain amount of patients will require insulin therapy.[21] According to the ADA/European Association for the Study of Diabetes (EASD), initiation of treatment with insulin in patients on oral antihyperglycaemic agents could be required in patients with an HbA1c level of 9.0% or greater, and should be started above 10%. Once insulin is started, long-acting insulin is mostly the option, with a 10 U or 0.1-0.2 U/kg administration once daily with titration to achieve appropriate fasting blood glucose levels. This type of insulin can be added to any regimen, being safe and effective when administered in conjunction with metformin, GLP1-RA, SGLT-2 inhibitors, or pioglitazone.[22] Biphasic insulin twice a day has shown to be more efficacious achieving a HbA1C < 7%. This is however associated with greater prevalence of hypoglycaemic events and of weight gain.[22]

Insulin dose adjustments are often required in patients with DKD. In fact, insulin clearance is highly dependent on GFR, and dose adjustment is necessary. Up to 50% reduction of total daily dose is recommended when eGFR falls between 10 and 50 mL/min/1.73 m^2, and 75% reduction is indicated for eGFR below 15 mL/min/1.73 m^2.[55]

New routes of administrations such as inhaled insulin have shown to be effective in achieving glycaemic control as well. Although it is a viable alternative in DKD patients,, drug absorption is significantly variable and this route of administration may cause small pulmonary function changes, making it contraindicated in patients with COPD and asthma.[104]

9 | CONCLUSION

Given the multiple concerns about the use of several antihyperglycaemic agents for the treatment of diabetes in patients with established DKD, we believe a strong effort towards patients and physician education should be implemented. Besides this education, we recommend individualizing each patient´s treatment, focusing on the potential long-term benefits of each agent and prospectively proceed to adjusting the dosage and use depending on the DKD stage to avoid any renal damage or stage progression. Considering the superiority of certain class of agents over others in protecting the kidney in the context of DKD, we also suggest a stronger interaction between nephrologists and endocrinologists to grant the selection of appropriate antihyperglycaemic agents in patients with established DKD at high risk for DKD progression. Nonetheless, positive results on renal outcome with certain class of agents warrant further investigation in these areas, as understanding the specific mechanisms driving renoprotection may lead to the discovery of new treatments focusing mainly on patients with established DKD.

ACKNOWLEDGEMENTS

AF is supported by NIH grants R01DK117599, R01DK104753, R01CA227493, U54DK083912, UM1DK100846, U01DK116101 and UL1TR000460 (Miami Clinical Translational Science Institute). AF also receives research support from Hoffman-La Roche and Boehringer Ingelheim.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

AUTHOR CONTRIBUTIONS

This manuscript has been read and approved by all the authors. All required authorship requirements have been met. SN, HDC, AND LAMC contributed with data generation, analysis and interpretation of the studies involved, and the preparation of the manuscript. AF realized the conception and design of the review, was involved in data generation, analysis, interpretation of the studies, and finished the preparation and critical revision of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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How to cite this article: Niezen S, Diaz del Castillo H, Mendez Castaner LA, Fornoni A. Safety and efficacy of antihyperglycaemic agents in diabetic kidney disease. *Endocrinol Diab Metab*. 2019;2:e00072. https://doi.org/10.1002/edm2.72