

Renal Outcomes Associated with the Use of Non-Insulin Antidiabetic Pharmacotherapy: A Review of Current Evidence and Recommendations

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Background: This study aims to discuss, summarize and compare the renal outcomes associated with non-insulin antidiabetic (AD) pharmacotherapy prescribed for patients with type 2 diabetes mellitus (T2DM).

Methods: A systematic search using predefined search terms in three scholarly databases, ScienceDirect, Google Scholar, and PubMed, was conducted. Original research articles published in the English language between 2012 and 2020 that reported renal outcomes associated with the use of non-insulin AD pharmacotherapy were eligible for inclusion. Review articles, meta-analysis studies, and conference proceedings were excluded. A study-specific data extraction form was designed to extract the author's name, country, publication year, study design, study population, objectives, key findings, and conclusions. A narrative review of the key findings that focused on renal outcomes and renal safety issues was conducted.

Results: Of the 18,872 results identified through the initial search, a total of 32 articles were included in this review. Of these, 18 of the included articles reported the renal outcomes of newer antidiabetic medications, eg, SGLT2 inhibitors and GLP-1 agonists. Eight studies focussed on the well-established antidiabetic medications, eg, metformin and sulphonylureas. The review reported three main types of the clinical impact of the prescribed AD on the renal outcomes: "renoprotective effects", "no additional risk" and "associated with a decline in renal parameters". Seventeen studies reported the renoprotective effects of AD, including SGLT2i studies (n=8), GLP1 studies (n=6), and DPP4i studies (n=3). The reported renoprotective effects included slowing down the GFR decline, improving albuminuria, and reducing renal adverse events. The "no additional risk" impact was reported in eight studies, including DPP4i studies (n=3), two SGLT2i studies (n=2), metformin studies (n=2), and one study involving pioglitazone. Furthermore, seven studies highlighted the "associated with a decline in renal parameters" effect. Of these, three involved SGLT2i, two with metformin, and one for each DPP4i and sulphonylurea.

Conclusion: More than half of the studies included in this review supported the renoprotective effects associated with the use of AD medications, particularly GLP-1A, SGLT2i, and some of the DPP4i. Further studies involving patients with various stages of chronic kidney disease (CKD) are required to compare AD medications' renal effects, particularly the newer agents.

Keywords: hypoglycemic agents, antidiabetic drugs, type 2 diabetes mellitus, renal effects, renal outcomes

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Introduction

Diabetes is a major public health disease that is increasingly becoming highly prevalent worldwide. The number of diabetic patients increased from 108 million to 422 million in the duration from 1980 to 2014.¹ Microvascular and macrovascular complications are common in diabetic patients. Diabetic kidney disease (DKD), also known as diabetic nephropathy, is a major microvascular complication that occurs in 20–40% of diabetic patients.² Screening for diabetic nephropathy is typically recommended 5 years after diagnosis in type 1 diabetes and should be considered at the time of diagnosis in type 2 diabetes.³ DKD can progress to end-stage renal disease (ESRD) requiring dialysis or kidney transplantation. In diabetic patients, the development of DKD raises the risk of mortality by at least fivefold compared to patients with normal renal function. In those who develop ESRD, the risk of death is increased up to 100-fold. This increased risk occurs due to higher rates of both cardiovascular and noncardiovascular events.⁴

Diabetic nephropathy is clinically diagnosed based on the presence of albuminuria and/or reduced eGFR to <60 mL/min/1.73 m² in the absence of signs or symptoms of other primary causes of kidney damage. Screening for albuminuria can be performed by urinary albumin-to-creatinine ratio (UACR) in a random spot urine collection.⁵ Albumin excretion rate higher than 30 mg per day or albumin/creatinine ratio (ACR) higher than 3 mg/mmol has been established as the marker for detecting kidney damage.⁶ The presence of albuminuria has been identified as a risk factor for further cardiovascular complications among patients with or without diabetes.⁷ Albuminuria and eGFR should be monitored regularly in diabetic patients to enable timely diagnosis and monitor the progression of DKD.

Intensive glycemic control has been shown in large randomized clinical trials to delay the onset and progression of DKD in diabetic patients.⁸ The choice of antidiabetic regimen for patients with type 2 diabetes mellitus (T2DM) relies on an interplay of patient characteristics, severity of hyperglycemia, and available therapeutic options. Pharmacological interventions used to improve glucose control include both oral and injectables. Pharmacotherapy is typically introduced using a stepwise approach starting with oral agents, followed by injectables such as glucagon-like peptide-1 analogs (GLP-1A) and insulin.⁵ Commonly prescribed classes of antidiabetic

(AD) medications include biguanides, thiazolidinediones, second-generation sulphonylureas. Several drugs have been introduced over the last 15 years to treat diabetes, including sodium-glucose cotransporter-2 inhibitors, dipeptidyl peptidase-4 inhibitors, and GLP-1 analogs. Interestingly, outcomes of recent trials have indicated that these drugs may directly improve renal function beyond changes in glycaemic control.⁴ This review, therefore, aims to discuss, summarize, and compare the renal outcomes associated with non-insulin antidiabetic (AD) pharmacotherapy prescribed for patients with T2DM.

Methods

Search Strategy and Identification of the Studies

Three scholarly databases, ScienceDirect, Google Scholar, and PubMed, were systematically searched to identify potentially relevant studies. The search terms used were “antidiabetic drugs OR antidiabetic medications AND renal outcomes OR kidney outcomes” or “hypoglycemic agents OR hypoglycemic drugs AND adherence OR compliance”. Individual names of agents and drug classes were considered to identify the potentially eligible articles. The abstracts of the eligible studies were screened for eligibility. Original research articles published between 2012 and 2020 in English and reported renal outcomes associated with the use of non-insulin antidiabetic drugs were eligible for inclusion. The searches were limited to the last eight years to provide a review of the most recently published evidence by incorporating all the relevant studies that have been published within this study period. Only studies that assessed the renal outcomes by quantitative clinical measures were eligible for inclusion. Review articles, meta-analysis, book chapters, and conference proceedings were excluded. Details for the inclusion criteria are presented in Table 1.

Study Selection and Data Extraction

Two independent reviewers reviewed the studies at the title and abstract level following the removal of duplicates. Eligible studies were identified and retrieved at full-text to consider them for inclusion. A series of meetings, in the beginning, at the middle, and end of the data extraction process were conducted to ensure consistency. The inclusion of a third reviewer was made to resolve any differences. Data were extracted from the selected studies using study-specific

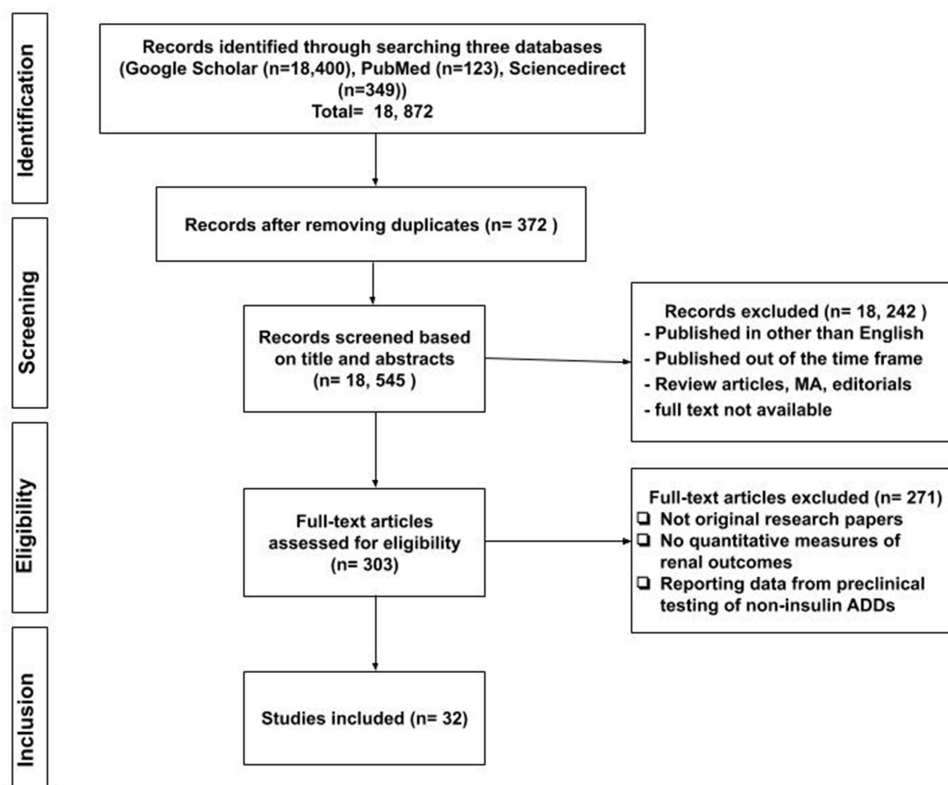
Table I Study Inclusion Criteria

No.	Category	Inclusion Criteria
1	Language of Publication	English
2	Year of Publication	2012–2020
3	Publication Type	Full-text original research article discussing the effects of AD medication on the renal system.
4	Outcomes Measures	Measuring patients' renal outcomes, either primary or secondary outcome measures.
5	Methodology	Clinical studies reported the renal outcomes of using non-insulin antidiabetic pharmacotherapy, either observational or experimental.
6	Patients	Adult patients with T2DM.

data extraction form to identify the author's name, country, year, study design, study population, length of follow-up, objectives, key findings, and conclusions. The relevant studies were grouped according to their AD medication classification. Reporting the key findings was carried out consistently, focusing on renal outcomes and renal safety issues. For articles that reported further analyses of the previously published clinical trials, the authors included the specific part of the findings related to renal outcome assessment. The flow chart describing the selection of the articles is illustrated in Figure 1.

Results

Of the 18,872 results identified through the initial search, a total of 32 articles were included in the review. There was a variation in the number of articles discussing the renal outcomes among various antidiabetic classes. Of these, 18 of the included articles reported the renal outcomes of newer antidiabetic medications, eg, SGLT2 inhibitors and GLP-1 agonists. Eight studies focussed on the well-established antidiabetic medications, eg, metformin and sulphonylureas. The included studies were observational, randomized controlled trials, and post hoc or secondary analyses.

**Figure 1** Flow chart on the selection of literature.

The review reported three main types of the clinical impact of the prescribed AD drugs on the renal outcomes. These included the “renoprotective effects”, “no additional risk, and “associated with a decline in renal parameters”. Seventeen studies reported the renoprotective effects of AD, including SGLT2i studies (n=8), GLP1 studies (n=6), and DPP4i studies (n=3). The reported renoprotective effects included slowing down the GFR decline, improving albuminuria, and reducing renal adverse events. The “no additional risk” impact was reported in eight studies, including DPP4i studies (n=3), two SGLT2i studies (n=2), metformin studies (n=2), and one study involving pioglitazone. Furthermore, seven studies highlighted the “associated with a decline in renal parameters” effect. Of these, three involved SGLT2i, two with metformin, and one for each DPP4i and sulphonylurea. The overall summary of the main characteristics and findings of the included studies have been presented in [Table 2](#)

Discussion

More than half of the studies included in this review supported the renoprotective effects associated with the use of antidiabetic medications, particularly GLP-1A, SGLT2i, and some of the DPP4i group. The demonstrated renoprotective effects included slowing down the GFR decline, improving albuminuria, and reducing renal adverse events. The remaining studies either showed no additional risk or minor and temporary decline in the renal function parameters. In general, no study reported the detrimental impact of antidiabetic medications on renal outcomes that outweighed any clinical benefit.

Metformin

Metformin is the first-choice antidiabetic medication for most of the cases, and it acts as insulin sensitizers. In our review, we found that diabetic patients with eGFR 45–60 mL/min/1.73 m² were reported to experience a lower risk of all-cause mortality with metformin administration.¹¹ Glomerular filtration rate is considered a good indicator in assessing the functionality of the renal system. In a large cohort study (n=124720), Christiansen et al reported that diabetic patients started on Metformin reported a lower risk of experiencing a severe decline of eGFR; however, the mild and moderate decline was common in those patients.¹⁰

There is conflicting evidence that suggests that acute kidney injury (AKI) is precipitated by metformin-associated lactic acidosis. Mariano et al reported that the use

of Metformin was associated with the occurrence of lactic acidosis, resulting in AKI that required renal replacement therapy (RRT).¹² However, the study reported a high survival rate following RRT. Moreover, most of the patients in this study experienced AKI when they had dehydration, shock, or oliguria. These conditions are previously known to result in increased Metformin levels, which has been proposed to precipitate lactic acidosis.⁴¹

On the contrary, an observational study involving 25,148 patients found no significant association of Metformin uses with an increased risk for AKI in terms of lactic acidosis.⁹ It is important to note that Mariano et al (2017) study was retrospective, which focused on the patients' survival rate, while Bell et al (2017) study focused more on the relationship between consumption of Metformin and the occurrence of AKI due to lactic acidosis. Further studies are required to explore the risk of Metformin for AKI in terms of lactic acidosis.

Sodium-Glucose Co-Transporter-2 Inhibitors (SGLT2i)

Sodium-glucose co-transporter-2 (SGLT2) inhibitors act by inhibiting the SGLT2 protein in the proximal convoluted tubule, stopping the reuptake of both sodium and glucose. The consequent increased urinary excretion of glucose improves glycemic control and weight loss, and the decreased reabsorption of sodium and glucose in the tubules promotes natriuresis and reducing blood pressure.⁴² In this review, more than half of the included studies involving SGLT2 inhibitors reported positive renal protective outcomes of SGLT2 inhibitors in patients. Three large multinational, randomized trials that were primarily designed to evaluate the cardiovascular outcomes of dapagliflozin, canagliflozin, and empagliflozin reported the renal endpoints as secondary outcomes. The strongest evidence emerged from the DECLARE-TIMI 58 trial, which secondarily investigated the renal effects of dapagliflozin in diabetic patients with existing cardiovascular disease or at high risk for cardiovascular disease (n=17160). In participants using dapagliflozin, there was a reduced risk of a sustained decline in eGFR, and the risk of ESRD or renal death.¹⁴ This positive nephroprotective role was reproduced in a similar patient population for canagliflozin from the CANVAS Program study (n=10142) and empagliflozin from a secondary analysis of the EMPA-REG OUTCOME study among Asian patients (n=1517).^{17,23} Although these are strong positive

Table 2 Summary of the Main Characteristics, Key Findings, and Conclusion of the Included Studies (n=32)

No.	Authors	Study Design, Participants, and Length of Follow-Up	Objectives	Findings	Conclusion
Metformin (n=4)					
1	Bell et al, 2017 ⁹ United Kingdom	Observational study with 25,148 patients from prescribing data (2003–2014). A survival rate at 28 days was assessed.	To examine the potential association between the use of Metformin and increased risk of acute kidney injury (AKI) in terms of lactic acidosis.	- There were 32.4 cases vs 44.9 cases of first AKI/1000 person-years in Metformin exposed and unexposed periods. - Current metformin usage showed no association with AKI incidence, HR 0.94 (p = 0.15). - After AKI, metformin users had a higher survival rate compared to no users (HR 0.81, p=0.006)	Metformin was not associated with increased AKI risk. Instead, it showed a higher survival rate after the incidence of AKI.
2	Christiansen et al, 2015 ¹⁰ Denmark & United Kingdom	Cohort study with 124,720 patients from different registries (2000–2011). Follow up period linked to GFR decline was 90 days.	To describe the prevalence of decline in eGFR among metformin initiators in two countries.	- About 9.0% and 25.2% of metformin initiators had declined eGFR values <60 mL/min/1.73m² whereas 0.3% and 0.4% had declined eGFR values <30 mL/min/1.73 in Denmark and the UK, respectively. - About 44% and 62% in Denmark and the UK, respectively, have continued Metformin after having their eGFR below 30 mL/min/1.73 m².	Severe decline of eGFR values is uncommon among the metformin initiators compared to mild and moderate forms. Even with the severe decline, patients were likely to continue their Metformin.
3	Ekstrom et al, 2012 ¹¹ Sweden	Observational study with 51,675 patients (2004–2010). Follow up was set at a mean of 3.9 years.	To evaluate the effectiveness and safety of metformin initiation in diabetic patients with varying degrees of renal function.	- The usage of Metformin was linked to a significant decrease in the risk of all-cause mortality (HR 0.87) in patients with eGFR 45–60 mL/min/1.73 m² compared to other OHA. - There was no increment in the risks of serious infection, acidosis, and all-cause mortality among the metformin group with eGFR 30–45 mL/min/1.73 m².	Metformin has demonstrated higher benefits compared to risks in diabetic patients with renal impairment.
4	Mariano et al, 2017 ¹² Italy	Retrospective analysis (2010–2015) involved 141,174 ICU diabetic patients on renal replacement therapy (RRT) and Metformin.	To determine the incidence and outcome of acute kidney injury (AKI)-Metformin Associated Lactic Acidosis (MALA) in patients treated with RRT.	- A total of 117 cases reported the incidence of AKI – MALA – RRT, and the survival rate was 78.3%. - Most of the admitted patients were dehydrated, affected by shock, and oliguria.	Early, continuous and efficient dialysis led to high survival rates among MALA-RRT cases.
Sodium Glucose Co-Transporter-2 (SGLT2) Inhibitor (n=13)					
5	Heerspink et al, 2020 ¹³ Multinational	Multinational observational cohort study involved 65,231 patients. Follow up was set at a mean of 14.9 months.	To determine the effect of sodium-glucose co-transporter-2 inhibitors (SGLT2i) in slowing the progression of chronic kidney disease in diabetic patients.	- SGLT2i initiators have experienced slower eGFR decline compared to other antidiabetic agents (p < 0.0001). - The incidence of composite kidney outcomes was also lower in the SGLT2i group than other antidiabetic agents (HR 0.49; p < 0.0001).	SGLT2i has a positive effect on slowing down chronic kidney disease progression and was associated with a lower risk of renal related adverse events.

(Continued)

Table 2 (Continued).

No.	Authors	Study Design, Participants, and Length of Follow-Up	Objectives	Findings	Conclusion
6	Mosenzon et al, 2019 ¹⁴ Multinational	Detailed analyses of renal outcomes of trial with 17,160 patients. Follow up was set at a median of 4.2 years.	To report renal outcomes of the DECLARE-TIMI 58 trial, including components of the cardiovascular and renal-specific composite outcomes	- Dapagliflozin participants had a lower risk for composite renal outcomes than the placebo (1.5% to 2.8%, HR 0.53) - Dapagliflozin reduced the risk of ESRD or renal-related death (0.1% vs 0.3%, HR 0.41) as compared to the placebo.	Dapagliflozin prevents and reduces DKD progression in patients with and without cardiovascular disease
7	Fiorotto et al, 2016 ¹⁵ Italy	Post hoc analysis included 166 diabetic patients with CKD stage 3. Follow up was set at 104 weeks.	To inspect changes in the urinary/creatinine ratio (UACR) of diabetic patients due to the long-term effects of dapagliflozin.	- Dapagliflozin 10 mg and 5 mg groups have shown a lower value of UACR (-57.2% vs -43.8%) compared to the placebo. - There were no significant differences in severe renal adverse effects among the dapagliflozin 5 mg, 10 mg, and placebo (1.9%, 1.8%, and 1.8%, respectively).	The use of dapagliflozin by CKD stage 3 diabetic patients has decreased their UACR levels without a rise in the significant adverse renal effects.
8	Fiorotto et al, 2018 ¹⁶ Italy	Randomized controlled trial with 321 patients. Follow up was set at 24 weeks.	To evaluate dapagliflozin's efficacy and safety for diabetic patients with moderate renal impairment (CKD 3A).	- Dapagliflozin group experienced a substantial decrease in HbA1c and a more significant reduction in eGFR (returned baseline 3-week post-treatment) relative to placebo. - There was no rise in frequent and serious adverse reactions (41.9% and 5.6%, respectively) relative to placebo groups (47.8% and 8.7%, respectively).	The use of dapagliflozin in diabetic patients with CKD 3A has shown more benefit relative to risk throughout treatment.
9	Kadowaki et al, 2019 ¹⁷ Japan	Post hoc analysis included 1517 Asian patients. Follow up was set at 164 weeks.	To determine the effects of empagliflozin on kidney among Asian patients with established CVD as part of the EMPA-REG OUTCOME® trial.	- Compared to placebo, empagliflozin was significantly associated with reduced risk of nephropathy (HR 0.64), microalbuminuria (HR 0.64), and renal death (HR 0.48). - Empagliflozin users have also experienced a lower eGFR decline rate and better UACR reduction (at week 12 and beyond) compared to the placebo group.	Asian patients on empagliflozin have experienced kidney protective effects compared to the placebo group.
10	Kashiwagi et al, 2015 ¹⁸ Japan	Randomized controlled trial (LANTERN study) with 165 patients. Follow up was set at a total of 52 weeks.	To investigate the safety and efficacy in the use of ipragliflozin by diabetic patients that have renal impairment.	- Statistically significant decreases in the level of HbA1c and FPG were observed in patients with mild-R1 but not in patients with moderate-R1. - Ipragliflozin has not been associated with any significant safety issues.	In patients with mild but not moderate renal impairment, ipragliflozin could improve glycemic control.

11	Wanner et al, 2016 ¹⁹ Multinational	Analysis of the secondary outcomes of the EMPA-REG OUTCOME trial that involved with 6185 patients. Follow up for reported key findings was adjusted at 48 months.	To investigate the long-term renal effects of empagliflozin on the secondary renal outcomes among patients with type 2 diabetes at high risk for cardiovascular events.	- Empagliflozin was associated with a lower incidence of worsening nephropathy (12.7% vs 18.8%) than a placebo. (HR 0.61; 95% P<0.001). - Empagliflozin group experienced a lower occurrence of doubling the serum creatinine level compared to placebo (1.5% vs 2.6%) with a significant relative risk reduction of 44%.	Empagliflozin was linked to lower clinically significant renal events correlated with slower development of kidney disease than placebo.
12	Lambers Heerspink et al, 2013 ²⁰ Canada, USA, and Netherlands	Randomized, placebo-controlled, double-blind trial with 75 subjects. Follow up was set at 12 weeks.	To compare dapagliflozin and hydrochlorothiazide (HCTZ) effects on glomerular filtration rate (GFR).	- The administration of dapagliflozin to the patients causes a higher reduction in GFR (−10.8% vs −3.4%) than HCTZ. - Both dapagliflozin and HCTZ were associated with decreased body weight.	Initiation of dapagliflozin can cause GFR and bodyweight reduction, thus having a diuretic-like effect.
13	Nadkarni et al, 2017 ²¹ USA	Propensity matched analysis involved 1584 SGLT2i users from two cohorts. Follow up was set at 14 months.	To investigate the risk of acute kidney injury in new SGLT2i users among patients with T2DM.	In both cohorts, SGLT2i users tend to have lower unadjusted hazards (HR 0.4; P = 0.01 and HR 0.5; P < 0.01, respectively) of acute kidney injury compared to the non-users.	The use of SGLT2i was not linked to increment in the risk of acute kidney injury among T2DM patients.
14	Mahaffey et al, 2019 ²² Multinational	Analysis of the results of the CREDENCE trial that involved 4401 participants. Follow-up was set at a median of 2.62 years.	To assess the outcomes of using canagliflozin in people with T2D, CKD with (secondary prevention), or without (primary prevention) preexisting CVD.	The risk of the primary composite renal outcome was consistently reduced with canagliflozin in both the primary and secondary prevention groups.	Canagliflozin showed protective renal outcomes in T2DM patients with no underlying CVD.
15	Perkovic et al, 2018 ²³ CANVAS Program (30 countries)	Two randomized controlled trials involved a total of 10,142 participants. Follow up was set at least 78 weeks (average 3–4 years).	To investigate the long-term effects of canagliflozin on various renal outcomes.	- Canagliflozin group has a lesser possible association with ESKD's composite outcomes, renal-related deaths compared to the placebo group (HR 0.53, 95% CI 0.33–0.84). - Canagliflozin receivers experienced a slower annual eGFR decline and 18% lower mean UACR than the placebo group.	Canagliflozin has been shown to have a possible renoprotective effect on long term use among T2DM patients.
16	Yamout et al, 2014 ²⁴ USA	Analysis of 4 randomised controlled trial results focused on a cohort of 1085 T2DM subjects with stage 3 CKD. Follow up for the reported renal outcome was set at 26 weeks.	To evaluate the safety of using canagliflozin in T2DM patients with stage 3 chronic kidney disease.	- During the early treatment with canagliflozin, there have been initial declines in eGFR, but the value then improved back towards the baseline over time. - Canagliflozin groups have a higher incidence of renal-related adverse effects (8.9 vs 3.7) than the placebo group.	Canagliflozin was generally well tolerated by the patients with T2DM and stage 3 CKD.

(Continued)

Table 2 (Continued).

No.	Authors	Study Design, Participants, and Length of Follow-Up	Objectives	Findings	Conclusion
17	Cherney et al 2020 ²⁵ Canada	Post hoc analyses of 2 randomized control trials (VERTIS SU & VERTIS MET) involved 1936 T2DM patients. Follow up was set at 104 weeks.	To assess the impact of ertugliflozin on eGFR and UACR compared to glimepiride or placebo/glimepiride.	• Ertugliflozin group showed lower values for eGFR decline at 104 weeks, although it was higher at 6 weeks. • Among patients with albuminuria, the ertugliflozin group was associated with consistently higher UACR reductions across the follow-up period of 104 weeks.	Despite the initial eGFR decline, ertugliflozin showed renoprotective effects of preserving eGFR and reducing UACR values at 104 weeks.
Dipeptidyl Peptidase IV Inhibitors (DPP4i) (n=7)					
18	Rosenstock et al. 2019 ²⁶ 27 countries	Randomized, placebo-controlled, multicenter noninferiority trial in 6979 patients. Follow up was set at a median of 2.2 years.	To assess the effect of linagliptin on renal outcomes in T2DM patients at high CV and kidney risk.	• There was no significant difference in the risk of developing the renal composite outcome in participants using linagliptin compared to those using a placebo (9.4 vs 8.8%, HR 1.04). • Linagliptin users had a significantly lower odds of albuminuria progression than the placebo group (35.3 vs 38.5%, HR 0.86).	Linagliptin was non-inferior to placebo on its impact on the renal outcomes among T2DM patients at high risk of CV and kidney events.
19	Groop et al, 2017 ²⁷ 12 countries	Randomized controlled trial (MARLINA-T2D trial) with 360 patients. Follow up was set at 24 weeks.	To investigate the renal effects of linagliptin among diabetic patients with albuminuria.	• Linagliptin recipients had a lower, nonsignificant change in UACR from baseline about 6.0% (P = 0.1954) compared to the placebo group. • There were no significant differences in the event of adverse effects and changes in eGFR between the two groups.	Among diabetic patients with kidney disease, linagliptin had no significant lowering of albuminuria.
20	Kim et al, 2016 ²⁸ Republic of Korea	Retrospective observational cohort study with 414 T2DM patients. Outcomes were reported at 1 and 4 years intervals.	To evaluate the renoprotective effects of DPP4i in terms of their impact on albuminuria and glomerular filtration rate (GFR) among diabetic patients.	• At 1 year, DPP4i was linked to a significant reduction in the average UACR among all patients. Those with macroalbuminuria showed reduced albumin levels. • There was a slower eGFR reduction rate among patients with microalbuminuria at 4 years, while it was reversed in the macro- or normoalbuminuric groups.	DPP4i treatment exerted renoprotective effects by reducing urine albumin excretion and alleviate the decline of eGFR in diabetic patients.
21	Mosenzon et al, 2017 ²⁹ Multinational	Randomised controlled trial (SAVOR-TIMI 53 Trial) involved 16,492 patients over two years follow up.	To investigate the presence of a protective effect in diabetic nephropathy by saxagliptin.	• Saxagliptin group experienced a significant reduction in the ACR level throughout the trial compared to the placebo. • No significant changes can be seen in the GFR and renal safety profile between the two groups.	Saxagliptin has shown benefit to the patients by improving ACR levels that were not linked to changes in the eGFR level.

22	Scott et al, 2018 ³⁰ Multinational	Randomised controlled trial (CompoSIT-R Study) with 613 T2DM patients on Metformin $\pm$ SU. Follow up was set at 24 weeks.	To compare the safety of sitagliptin in comparison with dapagliflozin among T2DM patients with mild renal insufficiency.	- Both sitagliptin and dapagliflozin groups have similar results regarding the percentage of the participants who experience eGFR decline. - Sitagliptin has shown lower percentages of drug-related adverse events than dapagliflozin (7.8% vs 13.7%).	Sitagliptin showed a similar impact on the eGFR with an overall better safety profile compared to dapagliflozin.
23	von Eynatten et al, 2013 ³¹ Boehringer Ingelheim Pharmaceuticals (USA & Germany)	Pooled analysis of six phases III clinical trials with 512 T2DM patients with microalbuminuria and hypertension. Outcomes were reported at 18 and 24 weeks intervals.	To assess linagliptin's renal safety in a T2DM cohort with two vascular risk factors, microalbuminuria, and hypertension.	- Linagliptin group showed no significant difference in the eGFR compared to the placebo group. - Linagliptin groups experience a minor reduction in UACR from baseline in comparison to the placebo group.	Among this high-risk cohort, linagliptin was generally well tolerated.
24	Cornel et al, 2016 ³² 38 countries	Post hoc analysis of randomized trial (TECOS) with 14,671 T2D patients and established cardiovascular disease. Outcomes were reported at a median period of 3 years.	To assess CKD outcomes in patients with T2D when treated with sitagliptin based on their baseline (eGFR) level.	- Sitagliptin group had slightly lower (eGFR) values compared to the placebo. - Sitagliptin group demonstrated a marginally lower (by 0.18 mg/g) mean UACR than participants receiving placebo.	The shown slight differences do not confer clinically significant impact of sitagliptin on CKD outcomes.
Glucagon-Like Peptide-1 Analogues (n= 6)					
25	Gerstein et al, 2019 ³³ 24 countries	Analysis of data from randomized controlled study (REWIND) with 9901 T2DM patients. Follow up was set at a median of 5.4 years.	To investigate the long-term effects of dulaglutide on renal outcomes in T2DM patients.	- Dulaglutide was associated with a lower incidence of the composite renal outcomes (17.1% vs 19.6%, HR 0.85, p=0.0004) compared to the placebo. - Dulaglutide was linked to a decrease in the incidence of the new macroalbuminuria (p<0.0001).	Long term use of dulaglutide was associated with renoprotective effects.
26	Tuttle et al, 2018 ³⁴ 9 countries	Randomized controlled trial (AWARD-7) with 577 T2DM patients. Outcomes were reported at 52 weeks.	To assess kidney-related safety of once-weekly dulaglutide compared with daily insulin in T2DM patients with moderate-to-severe CKD.	- Dulaglutide 0.75 mg and 1.5 mg showed higher eGFR levels compared to insulin glargine (p=0.009 and p=0.005, respectively). - Dulaglutide 0.75 mg and 1.5 mg showed no significant impact on UACR reduction compared to insulin glargine.	Dulaglutide was associated with attenuation in the (eGFR) decline compared to insulin glargine.
27	Marso et al, 2016 ³⁵ 20 countries	Randomised controlled trial (SUSTAIN-6) in 3297 T2DM patients at high CVD risk. Follow up was set at a median of 3.8 years.	To investigate the effect of semaglutide on renal outcome compared to placebo.	Semaglutide reduced the risk of new or worsening nephropathy (3.8% vs 6.1%, HR 0.64, P = 0.005) compared to placebo.	Semaglutide group experienced a lower incidence of renal adverse outcomes compared to the placebo.

(Continued)

Table 2 (Continued).

No.	Authors	Study Design, Participants, and Length of Follow-Up	Objectives	Findings	Conclusion
28	Bethel et al, 2019 ³⁶ Multinational	Analysis of data from a randomized controlled trial (EXSCEL) in 13,844 T2DM patients. Follow up was set at a median of 3.2 years.	To investigate the effect of exenatide on renal outcomes in diabetic patients.	- Overall composite renal outcomes were significantly reduced among exenatide users as per adjusted analyses. - There were no significant differences between exenatide and placebo in the levels of (eGFR) and the incidence of new macroalbuminuria as per intention to treat analyses.	Exenatide seems to have potential, although inconsistent overall impact on the renal outcomes when considered for T2DM patients.
29	Mann et al, 2017 ³⁷ 32 countries	Analysis of data from a randomized controlled trial (LEADER) involved 9340 T2DM patients. Follow up was set at a median of 3.84 years.	To investigate the impact of long-term use of liraglutide on renal outcomes in T2DM patients.	- Liraglutide had significantly lower macroalbuminuria rates than the placebo group (161 vs 215 patients, HR 0.74; P = 0.004). - Liraglutide group had similar rates of renal adverse events compared to the placebo group.	Liraglutide initiation has been associated with lower rates of diabetic kidney disease progression compared to the placebo group.
30	Muskiet et al, 2018 ³⁸ Netherlands	Analysis of data from a randomized controlled trial (ELIXA) involved 5978 T2DM patients. Outcomes were reported at 108 weeks.	Investigate the effect of lixisenatide on renal outcomes focusing on UACR measures.	- Lixisenatide was linked to significantly lower new-onset macroalbuminuria (HR 0.80; p=0.04) compared with placebo. - There were no significant differences between groups in the measured levels of eGFR decline or renal adverse events.	Lixisenatide showed an impact on reducing UACR in patients with macroalbuminuria and decreasing the risk of new-onset cases.
Thiazolidinediones (TZD), Acarbose, Sulphonylureas (SU) (n=2)					
31	Chen et al, 2016 ³⁹ Taiwan	A randomized, open-labeled, controlled study with 60 patients treated with Metformin and sulphonylureas (SU) therapy. Follow up was set at six months.	To evaluate the effect of adding pioglitazone on urinary albumin to creatinine ratio (UACR) and (eGFR) of diabetic patients, compared to acarbose.	- The Pioglitazone group had no significant differences in eGFR and UACR values compared to the acarbose group. - The Pioglitazone group was more prone to gain weight and had lower fasting blood glucose values than the acarbose group.	The addition of pioglitazone or acarbose to patients treated with SU and Metformin for six months did not show significant changes in eGFR and UACR.
32	Van Dalem et al, 2016 ⁴⁰ Netherlands	Population-based cohort study with 120,803 diabetic patients (2004–2012). Follow up was set at a mean of 3.7 years.	To assess the risk of hypoglycemia and the use of SU and its effect on renal function, compared to Metformin.	- Compared to Metformin, SU users experienced a significant increment of the hypoglycemia risk (aHR 2.50). - Hypoglycemia incidence was higher among patients with an eGFR rate lower than 30 mL/min/1.73 m².	SU for diabetic patients with lower eGFR should consider the possible increase in the risk of hypoglycemia.

evidence points, a point to consider is the varying definitions of the renal outcomes utilized in these trials. Apart from the cardiovascular safety trials, the CREDENCE trial (n=4401) was primarily designed to assess canagliflozin's renal safety in diabetic patients with preexisting renal disease.²² It reported reductions in the proportions of participants using canagliflozin who attained ESRD, RRT, or renal death. On the other hand, some studies showed a reduction in the renal parameters, either GFR or UACR, although these effects tended to be minor and reversible in many cases.^{15,20,24}

To explain the positive renal outcomes of SGLT2 inhibitors in diabetic patients, it is reasonable to say that SGLT2 inhibitors promote nephroprotection by direct and indirect mechanisms. The direct mechanisms involve osmotic diuresis in overloaded cases in synergy with the given diuretic therapy and the suppression of oxidative stress and inflammation pathways.⁴³ Meanwhile, the indirect mechanisms include the ability to reduce blood pressure, body fat, body weight in addition to the uricosuric effect.⁴³ In a clinical trial, dapagliflozin was found to reduce blood pressure and body weight near the values reported for hydrochlorothiazide, although different underlying mechanisms exert diuretic effects.²⁰ As a consequence of reduced-sodium and glucose reabsorption in the tubules, SGLT2i enhances sodium and chloride delivery to the macula densa, resulting in the increased local secretion of vasoconstrictors that decrease the intraglomerular pressure and decrease the risk of hyperfiltration.⁴⁴ SGLT2i showed a remarkable nephroprotective effect by reversing the afferent arteriole's vasodilatation to reduce the albumin excretion.⁴⁴ Therefore, SGLT2i has been shown to mitigate two of the early pathophysiological mechanisms of DKD, hyperfiltration, and glomerular hypertension. The main precautions related to the use of SGLT2i over different eGFR values should also be emphasized where overall it should not be started at <60 and to be discontinued when it is below 45 mL/min/1.73 m² taking into account the minimum glycemic impact at this level.⁴⁴ Recent evidence suggest to consider SGLT2i treatment if eGFR is 30 to <90 mL/min/1.73 m².⁴⁵ A recent real-world data analysis has highlighted that although SGLT2i use was not linked to an increase in AKI's risk, increased reduction in eGFR was observed among patients with relatively reduced eGFR levels.⁴⁶ As discussed with cardiovascular outcomes,⁴⁷ it seems that relatively more evidence supports empagliflozin compared to other SGLT2i such as dapagliflozin and canagliflozin.⁴⁴

Dipeptidyl Peptidase 4 Inhibitors (Dpp4i)

Dipeptidyl peptidase IV (DPP4) inhibitors, also known as gliptins, act by several mechanisms: slowing down the gastric emptying and reducing postprandial glucagon. In our review, we included seven articles for this class of AD medication. Three studies reported positive outcomes associated with DPP4 inhibitors, while the remaining four studies showed no additional risk (n=3) or insignificant difference in eGFR decline (n=1) with the use of DPP4 inhibitors. A cohort study that assessed several types of DPP4 inhibitors among diabetic patients had identified a reduction in average ACR in macroalbuminuric patients while in microalbuminuria, the rate of eGFR reduction was alleviated.²⁸ Patients taking linagliptin in two trials have shown no significant change in eGFR, proving that there was neither improvement nor exacerbation of the condition.^{27,31} However, Rosenstock et al reported a smaller risk for albuminuria progression in diabetic patients using linagliptin compared to those on placebo.²⁶ Although there were no significant changes in eGFR of diabetic patients with saxagliptin, Mosenzon et al reported a reduction in the ACR in their trial (n=16492).²⁹ A randomized controlled trial that administered sitagliptin to the patients also reported that the sitagliptin group was found to have a lower incidence of adverse events than dapagliflozin.³⁰ Another randomized trial supported the safety of sitagliptin use among CKD patients, which reported no clinically significant effect of sitagliptin on CKD progression among 14,671 T2D patients.³²

DPP4i plays a significant role in glucose metabolism. It rapidly degrades GLP-1, an incretin hormone secreted postprandially, which stimulates the pancreatic GLP-1 receptor. This stimulation results in insulin secretion from β -cells and also inhibits glucagon secretion from α -cells.⁴⁸ DPP4 exists in several tissues, although its highest level is found in the kidneys, increasing diabetic nephropathy. Studies revealed that the use of DPP4i resulted in a nephroprotective effect via glycemic control. Additionally, the inhibition of DPP4 showed a renoprotective effect through other pathways such as reducing oxidative stress, inflammation and ameliorating renal fibrosis.⁴⁹ Moreover, the use of DPP4 inhibitors in T2D patients induced natriuresis,⁵⁰ which might positively affect renal parenchymal hypertension.⁵¹ In general, most of the findings from the reviewed articles support the positive effects of DPP4i on albuminuria and reduce ACR in T2D patients.

Glucagon-Like Peptide-I Analogues (GLP-1A)

Although only six of the included studies involved GLP-1A, all these studies showed potential renoprotective effects of GLP-1A. Liraglutide, an example of GLP-1A that acts by stimulating the release of insulin into the circulation, increasing urinary sodium excretion and decreasing urinary albumin excretion, has been reported to maintain the impact on reducing macroalbuminuria over approximately four years in a secondary analysis of the data of LEADER trial.³⁷ Considering that macroalbuminuria is linked to the incidence of cardiovascular events, so this could be one of the possible mechanisms for GLP-1A to show desirable cardiovascular outcomes.^{7,52} As discussed in cardiovascular outcome trials, it seems that relatively more strong evidence supports liraglutide than other GLP-1A, such as semaglutide and exenatide.^{44,45} Another GLP-1A, dulaglutide, showed positive outcomes in two studies. It reduced the predefined composite renal endpoint and had a significantly lower incidence rate of macroalbuminuria than the placebo in the REWIND trial.³³ It also reduced the decline of GFR following 52 weeks of therapy in Tuttle et al study.³⁴ Similar positive findings were reported with another two GLP-1As, semaglutide and exenatide, in which both medications reduced the incidence and progression of DKD in patients with T2DM.^{35,36} In the ELIXA trial,³⁸ lixisenatide, a GLP-1A, was compared to placebo and found to reduce the progression of ACR in macroalbuminuric patients. It also had a lower risk for new-onset macroalbuminuria after adjusting for HbA1c. In addition to their effect in lowering blood glucose, GLP-1As reduce blood pressure, insulin levels, and weight loss. With the natriuretic effect of GLP-1As, these factors may account for their beneficial effect on the renal system.⁵³ Moreover, GLP-1As have been reported to suppress kidney fibrosis.⁵⁴ Although these findings show great promise for diabetic patients, the ability of this group of ADD to retard ESRD progression is yet to be explored.⁵⁴

Many other oral antidiabetic classes had also been studied in some of the included articles such as pioglitazone, which is classified under the class of thiazolidinediones that act by improving the sensitivity of insulin receptors while also reducing the production of glucose by the liver. Chen et al found out that patients taking pioglitazone showed no significant differences in terms of GFR and ACR compared to a group of patients that

took acarbose, an α -glucosidase inhibitor, that acts by slowing down the breakdown of carbohydrates in the intestine.³⁹ Further studies are required to make a conclusive statement regarding the effects of pioglitazone and also acarbose on the renal system. In a population-based study, the use of sulphonylureas (SU) was linked to a high risk of hypoglycemia among T2D patients with advanced chronic kidney disease (eGFR < 30 mL/min/1.73 m²).⁴⁰ The researchers concluded that sulphonylureas should not be prescribed to this group of patients, unless with caution. It is worth to mention here that studies showed that hypoglycemia is associated with cardiac disturbances, increasing the risk for morbidity and mortality. Moreover, CKD is known as an independent risk factor for hypoglycemia; it also intensifies the risk already present in diabetic patients.^{55,56}

Recommendations

Overall, AD pharmacotherapy's potential renoprotective effects were reported at various evidence levels for SGLT2i, GLP-1A, and DPP4i. Among the incretin-based therapies (DPP4i & GLP-1A), GLP-1A had relatively more pronounced glucose-independent effects on the renal risk factors among T2DM patients such as decreasing obesity, dyslipidemia, and glomerular hyperfiltration.⁵⁷ Therefore, it appears that more substantial evidence of renoprotective effects has been shown in studies with the use of SGLT2i and GLP-1A compared to those with DPP4i. As per the recent guidelines of the European Association for the study of Diabetes, the nephroprotective effects were reported for three SGLT2i (empagliflozin, canagliflozin, and dapagliflozin) and two GLP-1A (liraglutide and semaglutide).⁴⁵ Also, suppression of GFR decline has been more clearly shown in studies with SGLT2i compared with GLP-1A. Moreover, SGLT2i was associated with the earlier and more consistent incidence of renoprotective effects than GLP-1A, attributed mainly to the underlying hemodynamic changes.⁵⁸ The SGLT2i-associated renoprotective effects have been highlighted as a key mechanism for the reported cardiovascular benefits.⁴³ Meanwhile, the potential renoprotective effects of GLP-1A were attributed mainly to its impact on mitigating the progression of atherosclerosis-related vascular disease.⁵² Consistently with our review findings, there are recent recommendations to consider either SGLT2i or GLP-1A as add on to metformin in patients who had mainly underlying atherosclerotic cardiovascular disease, and to consider SGLT2i first, in patients who had underlying chronic kidney disease and reduced heart failure, to

be followed by GLP-1A if needed.⁴⁴ Furthermore, the most recent American standards of medical care in diabetes have highlighted the role of SGLT2i in T2DM patients and DKD, particularly among those with urinary albumin >300 mg/g creatinine to mitigate the progression of CKD and cardiovascular events. Whereas GLP-1A is recommended for those CKD patients at an increased CVD risk to reduce the risk of cardiovascular events and the risk of albuminuria progression.⁵⁹ With close consideration of the bidirectional relationship between kidney and cardiovascular events among patients with diabetes,⁶⁰ those antidiabetic therapies with a favorable impact on renal and cardiovascular outcomes will play a crucial role in reshaping the way of mitigating diabetes complications.

Conclusion

More than half of the studies included in this review supported the renoprotective effects associated with the use of AD medications, particularly GLP-1A, SGLT2i, and some of the DPP4i. The renal outcomes' impact should be translated into practice with consideration to the baseline renal function and the risk of diabetes complications such as hypoglycemia. There are several recommendations for optimizing the use of SGLT2i and GLP-1A in the care of diabetes patients at increased risk of renal or cardiovascular events. Furthermore, owing to the differences in the study designs of included studies, there are several recommendations for optimizing the use of SGLT2i and GLP-1A in the care of diabetic patients who are the increased risk of renal or cardiovascular events. Further analysis and comparison between agents of the same class are also encouraged. Finally, renal outcomes were mostly reported as secondary outcomes or part of the post hoc analysis; it is suggested that future trials setting the extent of nephroprotection as the sole primary outcome will strengthen the evidence of the renal outcomes of various AD pharmacotherapies.

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Disclosure

The authors report no conflicts of interest for this work.

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