

The treatment of type 2 diabetes in the presence of renal impairment: what we should know about newer therapies

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Abstract: Worldwide, an estimated 200 million people have chronic kidney disease (CKD), the most common causes of which include hypertension, arteriosclerosis, and diabetes. Importantly, ~40% of patients with diabetes develop CKD, yet evidence from major multicenter randomized controlled trials shows that intensive blood glucose control through pharmacological intervention can reduce the incidence and progression of CKD. Standard therapies for the treatment of type 2 diabetes include metformin, sulfonylureas, meglitinides, thiazolidinediones, and insulin. While these drugs have an important role in the management of type 2 diabetes, only the thiazolidinedione pioglitazone can be used across the spectrum of CKD (stages 2–5) and without dose adjustment; there are contraindications and dose adjustments required for the remaining standard therapies. Newer therapies, particularly dipeptidyl peptidase-IV inhibitors, glucagon-like peptide-1 receptor agonists, and sodium-glucose cotransporter-2 inhibitors, are increasingly being used in the treatment of type 2 diabetes; however, a major consideration is whether these newer therapies can also be used safely and effectively across the spectrum of renal impairment. Notably, reductions in albuminuria, a marker of CKD, are observed with many of the drug classes. Dipeptidyl peptidase-IV inhibitors can be used in all stages of renal impairment, with appropriate dose reduction, with the exception of linagliptin, which can be used without dose adjustment. No dose adjustment is required for liraglutide, albiglutide, and dulaglutide in CKD stages 2 and 3, although all glucagon-like peptide-1 receptor agonists are currently contraindicated in stages 4 and 5 CKD. At stage 3 CKD or greater, the sodium-glucose cotransporter-2 inhibitors (dapagliflozin, canagliflozin, and empagliflozin) either require dose adjustment or are contraindicated. Ongoing trials, such as CARMELINA, MARLINA, CREDENCE, and CANVAS-R, will help determine the position of these new therapy classes and if they have renoprotective effects in patients with CKD.

Keywords: DPP-IV inhibitor, GLP-1RA, SGLT-2 inhibitor, PK, chronic kidney disease, renal impairment

Introduction

Chronic kidney disease (CKD) can adversely affect the pharmacokinetics (PK) or pharmacodynamics (PD) of some therapies.¹ Thus, in order for clinicians to make informed choices, it is important to understand how: 1) the use of glucose-lowering therapies is affected by renal impairment; 2) treatment regimens may need to be modified and how these treatments may impact on CKD outcomes; and 3) the importance of safety across the spectrum of CKD.

Worldwide, an estimated 200 million people have CKD,² a long-term condition that may lead to renal failure and, if left untreated, to premature death. CKD is characterized

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Table 1 National Kidney Foundation criteria for CKD

Criteria (either present for ≥ 3 months)	Abnormalities of kidney structure or function
Markers of kidney damage (one or more)	Albuminuria (AER ≥ 30 mg/24 h; ACR ≥ 30 mg/g [≥ 3 mg/mmol]) Urine sediment abnormalities Electrolyte and other abnormalities due to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation
Decreased GFR	GFR < 60 mL/min/1.73 m ² (GFR categories CKD 3a–CKD 5)

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Abbreviations: ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; CKD, chronic kidney disease; GFR, glomerular filtration rate.

by the presence of kidney damage, indicated by albuminuria and/or a gradual loss of kidney function (estimated glomerular filtration rate [eGFR]) over time.² Common causes of CKD include hypertension,³ atherosclerosis,⁴ and diabetes.⁵ Furthermore, CKD is associated with an elevated risk of death from cardiovascular (CV) disease.⁶ Kidney Disease: Improving Global Outcomes criteria and associated CKD stages are summarized in Tables 1 and 2, respectively.⁷

Approximately 40% of patients with diagnosed or undiagnosed diabetes have CKD⁸ and, in the absence of monitoring for and effective treatment of renal function, CKD can develop insidiously.⁹ Pathological changes in the kidney include increased glomerular basement membrane thickness, formation of microaneurysms, and mesangial nodules.¹⁰ The current estimates show a global prevalence of 415 million adults with diabetes,¹¹ with type 2 diabetes (T2D) accounting for ~90% of these patients,¹² CKD in diabetes is, thus, a significant health problem. Atherosclerosis is also an associated condition, leading to narrowing of arterial walls

Table 2 Staging of CKD

GFR grade	GFR (mL/min/1.73 m ²)	Terms
1	≥ 90	Normal or high ^a
2	60–89	Mildly decreased ^a
3a	45–59	Mildly to moderately decreased ^b
3b	30–44	Moderately to severely decreased
4	15–29	Severely decreased
5	< 15	Kidney failure

Notes: ^aIn the absence of evidence of kidney damage, neither GFR grade 1 nor grade 2 fulfills the criteria for CKD. ^bRelative to young adult level. Reprinted from *Kidney Int Suppl*, 3(1), Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease, 1–163, Copyright (2013), with permission from Elsevier.⁷

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

and subsequent high blood pressure.¹⁰ Diabetic nephropathy is generally, but not always, preceded by albuminuria, defined as proteinuria of > 500 mg/day.¹⁰ In fact, there is evidence that intensively improving blood glucose control through pharmacological intervention can reduce the incidence and progression of CKD in people with diabetes. The UK Prospective Diabetes Study found a reduced risk of progressive kidney disease with intensive glycemic control, apparent from a 34% reduction in albuminuria, 67% reduction in the proportion of patients who had a twofold increase in plasma creatinine, and 74% reduction in the proportion of patients who had doubling of plasma urea.¹³ In addition, the Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation trial determined that intensive glucose control significantly reduced the risk of progression to stage 5 CKD by 65%, microalbuminuria by 9%, and macroalbuminuria by 30%.¹⁴ In the Steno-2 study, patients with T2D and microalbuminuria receiving intensive therapy (compared with conventional therapy) had a significantly lower risk of nephropathy (hazard ratio: 0.39, 95% confidence interval [CI]: 0.17–0.87; $P < 0.003$).¹⁵

A recent meta-analysis demonstrated that combination therapies are effective in improving glycemic control, with some combinations of metformin and newer drug classes (specifically, dipeptidyl peptidase-IV [DPP-IV] inhibitors, glucagon-like peptide-1 receptor agonists [GLP-1RAs], and sodium-glucose cotransporter-2 [SGLT-2] inhibitors) providing glycemic control without increasing the risk of hypoglycemia or weight gain.¹⁶ Indeed, many current treatment guidelines now advocate the use of these newer therapies in multiple stepwise combinations.¹⁷

As previous reviews have already investigated the impact of conventional glucose-lowering therapies on CKD,^{18,19} this review will primarily focus on the newer therapies (DPP-IV inhibitors, GLP-1RAs, and SGLT-2 inhibitors), mechanisms by which CKD affects the use of T2D therapies, place of these therapies in CKD treatment, and their potential renoprotective effects.

T2D therapies and CKD

Conventional glucose-lowering therapies

Conventional glucose-lowering therapies include metformin, sulfonylureas, thiazolidinediones, meglitinides, and insulin.

Apart from pioglitazone, a thiazolidinedione,²⁰ other conventional therapies must be reduced or withdrawn as eGFR declines due to increased risk of lactic acidosis (in the case of metformin) and hypoglycemia (in the case of sulfonylureas, meglitinides [such as repaglinide], and insulin).^{21–33} Their use in CKD is described below and summarized in Table 3.

Metformin

Metformin may be used without dose adjustment in patients with stage 2 CKD. With dose adjustment, metformin may be used in patients with stage 3a CKD, but only in the absence of other conditions, such as liver dysfunction,³⁵ CV disease,³⁶ and renal disease,³⁶ which may increase the risk of lactic acidosis. Renal function must be closely monitored every 3–6 months and, if eGFR falls to <45 mL/min/1.73 m², metformin administration must be stopped.²¹ Current UK National Institute for Health and Care Excellence guidelines suggest stopping if eGFR falls to <30 mL/min/1.73m².³⁷ Clinical data on the risk of lactic acidosis in metformin-treated patients with CKD are currently limited.³⁸

Sulfonylureas

Patients with CKD who are treated with glipizide, glibenclamide, gliclazide, and glimepiride require careful monitoring. Moreover, these sulfonylureas are contraindicated in patients with stage 4 CKD.^{22–25} The PK and/or PD of glipizide may be altered in patients with impaired renal function; initial and maintenance dosing should, therefore, be conservative to avoid hypoglycemic episodes.²² Glibenclamide should be used cautiously in patients with stages 2 and 3 CKD; however, in long-term clinical trials, patients with renal impairment have been treated adequately at reduced doses with frequent monitoring.²³ Likewise, in long-term clinical trials, patients

with renal impairment have also been treated adequately using gliclazide at reduced doses with frequent monitoring.²⁴ In the case of glimepiride, in patients with low creatinine clearance (CrCl), there is a trend for glimepiride clearance to elevate and serum concentrations to diminish.²⁵

Meglitinides

The meglitinides, such as repaglinide, are short-acting. Patients with CKD ranging from stages 3b to 5 require careful management.²⁶ Repaglinide is mostly metabolized by the liver and, with dose adjustment, may be used in patients with CKD.²⁶ In a clinical trial, after 5 days of treatment with repaglinide, there was a twofold increase in exposure (area under the curve [AUC]) and half-life in patients with stage 4 CKD compared with individuals with normal renal function.²⁶

Thiazolidinediones

Of the thiazolidinedione family, only pioglitazone is generally available due to safety concerns with other agents in this class. No dose adjustment is required with impaired renal function (stages 2–5 CKD), as pioglitazone is metabolized mainly by the liver.^{20,39} No information is available for patients undergoing dialysis; therefore, pioglitazone should not be used in this setting. Plasma concentrations of pioglitazone and its metabolites in patients with CKD are lower than those

Table 3 The use of conventional glucose-lowering therapies in chronic kidney disease (based on European Union label)

Therapy	Licensed dose	eGFR (mL/min/1.73 m ²) (associated stage)				
		60–89 (stage 2)	45–59 (stage 3a)	30–44 (stage 3b)	15–29 (stage 4)	<15 (stage 5)
Metformin ²¹	500 mg or 850 mg bid or tid	✓	–	✗	✗	✗
Glipizide ^{a,22}	2.5–20 mg daily	–	–	–	✗	NS
Glibenclamide ^{23,a}	2.5–15 mg daily	–	–	–	✗	NS
Gliclazide ^{24,a}	40–320 mg daily	–	–	–	✗	NS
Glimepiride ^{25,b}	1–6 mg daily	–	–	–	✗	NS
Repaglinide ²⁶	0.5–16 mg daily	✓	✓	– ^c	–	–
Pioglitazone ²⁰	15–45 mg od	✓	✓	✓	✓	✓ ^d
Acarbose ^{34,e}	50 mg tid	✓	✓	✓	✗ ^e	✗
NPH insulin ^{27,f}	According to the requirement of the patient	–	–	–	–	–
Insulin glargine ^{28,g}	According to the requirement of the patient	–	–	–	–	–
Insulin detemir ^{29,g}	According to the requirement of the patient	–	–	–	–	–
Insulin degludec ^{30,g}	According to the requirement of the patient	–	–	–	–	–
Insulin lispro ^{31,h}	According to the requirement of the patient	–	–	–	–	–
Insulin glulisine ^{32,h}	According to the requirement of the patient	–	–	–	–	–
Insulin aspart ^{33,h}	According to the requirement of the patient	–	–	–	–	–

Notes: ✓ Indicated and no dose adjustment required. “–” Indication may be variable/consider dose reduction, frequent monitoring and relevant health status. ✗ Contraindicated. ^aSecond-generation SU. ^bThird-generation SU. ^cPatients with severely impaired renal function (CrCl: 20–39 mL/min) showed a significant twofold increase in AUC and t_{1/2} as compared with individuals with normal renal function. ^dNo dose adjustment required if eGFR is >4 mL/min. ^eAvoided if eGFR <25 mL/min/1.73 m². ^fIntermediate-acting insulin. ^gLong-acting insulin. ^hFast-acting insulin.

Abbreviations: AUC, area underneath the curve; bid, twice daily; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; NPH, neutral protamine Hagedorn; NS, not stated; od, once daily; SU, sulfonylurea; t_{1/2}, half-life; tid, three times daily.

observed in individuals with normal renal function, but the parent compound shows comparable apparent clearance.²⁰ Edema occurs in ~5% of patients treated with pioglitazone in monotherapy or combination therapy.⁴⁰ Although there have been concerns over CV risk,⁴¹ a recent study showed that pioglitazone was not associated with any increase in CV adverse events (AEs).⁴¹

Alpha-glucosidase inhibitors

The alpha-glucosidase inhibitor acarbose has gastrointestinal side effects associated with its use, including flatulence, soft stools, and abdominal discomfort.^{34,42} Acarbose is excreted unaltered by the renal system and should not be initiated in patients with stage 4 CKD.³⁴

Amylin analogs

Amylin analogs, such as pramlintide, are commonly used in the US. Pramlintide has limited side effects but a small proportion of patients may have intolerable nausea despite receiving the lowest doses.⁴³ The dosing requirements for pramlintide are not altered in patients with stages 2–4 CKD.⁴³ Pramlintide has not been studied in patients with stage 5 CKD.⁴³

Dopamine agonists

Dopamine agonists, such as bromocriptine, are commonly used in the US. Common side effects of bromocriptine include nausea, asthenia, constipation, dizziness, and rhinitis.⁴⁴ No PK studies have been conducted in patients with renal impairment.⁴⁵ Although the kidney is a minor pathway for elimination of bromocriptine, careful monitoring should be undertaken in patients with renal impairment.⁴⁵

Insulin

Classes of insulin include intermediate-acting (neutral protamine Hagedorn insulin, indicated for basal coverage), long-acting (glargine 100 units/mL²⁸ and 300 units/mL [U300],⁴⁶ detemir²⁹ and degludec³⁰ indicated for basal coverage), and fast-acting (lispro,⁴⁷ glulisine,⁴⁸ and aspart,⁴⁹ indicated for prandial coverage). CKD may reduce insulin requirements dramatically and increase the risk for hypoglycemia in patients.⁵⁰ Insulin dose, therefore, needs to be adjusted on an individual basis.

In patients with CKD, glargine requirements may be diminished because of reduced insulin metabolism;^{28,46} the high concentration of insulin (U300) results in different PK and PD profiles, but both concentrations have been shown to be safe in patients with renal failure.^{46,51,52} In a clinical study,

the PK of detemir did not significantly differ in patients with stages 3–4 CKD compared with healthy individuals.⁵³ Likewise, in one clinical study, renal impairment did not have a significant effect on maximum concentration (C_{max}), apparent clearance, or AUC_{0-120h} of single-dose degludec.^{30,54}

The glucodynamic response to insulin lispro is not affected by renal impairment.^{31,47} Glulisine requirements may be reduced in the presence of renal impairment.³² In patients with type 1 diabetes, renal impairment (stages 2–5 CKD) did not affect the PK of aspart in a clinically significant manner.^{33,55}

Newer therapies

DPP-IV inhibitors, GLP-1RAs, and SGLT-2 inhibitors are the most recent classes of agents licensed for use in T2D in Europe. The use of newer therapies in CKD is described below and summarized in Table 4.

DPP-IV inhibitors

DPP-IV inhibitors, such as sitagliptin, vildagliptin, saxagliptin, alogliptin and linagliptin, reduce the physiological breakdown of native GLP-1, which increases the secretion of insulin and promotes satiety, effectively decreasing blood glucose levels.⁷⁰ A meta-analysis has shown that DPP-IV inhibitors are effective in lowering glycated hemoglobin (HbA_{1c}) in patients with T2D and stages 3–4 CKD (–0.52%, 95% CI: –0.64 to –0.39).⁷¹ Despite associations with AEs that include nasopharyngeal symptoms, headaches, angioedema,^{72,73} and pancreatitis,⁷² meta-analyses showed low prevalence of such AEs.^{74,75}

DPP-IV inhibitors are metabolized and eliminated in a number of different ways. Their mode of action (MOA) and elimination, as well as PK and safety, are described in Table 5.

Sitagliptin

Sitagliptin undergoes limited hepatic metabolism; ~80% of the dose is excreted renally, and there is a low, reversible protein binding in the plasma (38%).⁷⁶

The TECOS study showed that sitagliptin was noninferior to placebo for the primary composite CV outcome of CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina (hazard ratio 0.98, 95% CI: 0.88–1.09; $P < 0.001$).⁸³ In addition, no significant differences between the placebo and sitagliptin group in incidences of pancreatic cancer ($P = 0.32$), acute pancreatitis ($P = 0.07$), or hospitalization for heart failure ($P = 0.98$) were reported.⁸³ In T2D patients, sitagliptin has also been

Table 4 Newer glucose-lowering therapies and data regarding their use in CKD (based on European Union label)

Drug class	eGFR (mL/min/1.73 m ²) (associated stage)						
	Therapy	Licensed dose	60–89 (stage 2)	45–59 (stage 3a)	30–44 (stage 3b)	15–29 (stage 4)	<15 (stage 5)
DPP-IV inhibitors	Sitagliptin ⁵⁶	25–100 mg daily	✓	✓ ^a	–	–	–
	Vildagliptin ⁵⁷	50–100 mg daily	✓	✓ ^a	–	–	–
	Saxagliptin ⁵⁸	2.5–5 mg daily	✓	–	–	–	× ^b
	Linagliptin ⁵⁹	5 mg daily	✓	✓	✓	✓	✓
	Alogliptin ⁶⁰	6.25–25 mg daily	✓	– ^a	–	–	–
GLP-IRAs	Exenatide bid ⁶¹	5–10 µg sc injection bid	✓	✓ ^a	–	×	×
	Exenatide ow ⁶²	2 mg sc injection ow	✓	✓ ^a	×	×	×
	Lixisenatide ⁶³	10–20 µg sc injection od	✓	✓ ^{a,c}	–	×	×
	Liraglutide ⁶⁴	0.6–1.8 mg sc injection od	✓	✓	✓	×	×
	Albiglutide ⁶⁵	30–50 mg sc injection ow	✓	✓	✓	×	×
	Dulaglutide ⁶⁶	0.75–1.5 mg sc injection ow	✓	✓	✓	×	×
SGLT-2 inhibitors	Dapagliflozin ⁶⁷	5–10 mg od	✓	×	×	×	×
	Canagliflozin ⁶⁸	100–300 mg od	✓	– ^d	×	×	×
	Empagliflozin ⁶⁹	10–25 mg od	✓	– ^e	×	×	×

Notes: ✓ Indicated and no dose adjustment required. “–” Indication may be variable/consider dose reduction, frequent monitoring and relevant health status. × Contraindicated. ^aNo dose adjustment required if eGFR is >50 mL/min. ^bIn patients requiring hemodialysis. ^cContraindicated if GFR <50 mL/min. ^dIn patients tolerating canagliflozin whose eGFR falls persistently below 60 mL/min/1.73 m² or CrCl 60 mL/min, the canagliflozin dose should be altered to or maintained at 100 mg od. ^eIn patients tolerating empagliflozin whose eGFR falls persistently below 60 mL/min/1.73 m² or CrCl below 60 mL/min, the dose should be altered to or managed at 10 mg od.

Abbreviations: bid, twice daily; CKD, chronic kidney disease; CrCl, creatinine clearance; DPP-IV, dipeptidyl peptidase-IV; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; GFR, glomerular filtration rate; od, once daily; ow, once weekly; sc, subcutaneous; SGLT-2, sodium-glucose cotransporter-2.

shown to reduce significantly urinary albumin excretion ($P < 0.0001$).⁸⁴

One PK study in patients without T2D showed that, compared with healthy controls, plasma sitagliptin AUC levels in patients with stages 2–5 CKD were increased by factors of 1.6–4.5.⁷⁷ C_{max} was moderately increased, and concentration at 24 hours increased as severity of CKD increased. Time to C_{max} was significantly increased in patients with stage 5 CKD, and the half-life increased with increasing severity of CKD. For patients with stages 2–4 CKD, clearance rates were 0.18–0.71 mL/min.⁷⁷

In treatment, patients with stage 2 CKD and stage 3 CKD (if eGFR is ≥ 50 mL/min) require no dose adjustment. For stage 3 CKD and an eGFR of <50 mL/min, the sitagliptin dose should be reduced to 50 mg once daily (od). For patients with stages 4–5 CKD, including those undertaking hemodialysis or peritoneal dialysis, the dose should be decreased to 25 mg od. Treatment can be administered regardless of dialysis time.⁵⁶

Vildagliptin

Vildagliptin is metabolized via four metabolic pathways before excretion.⁸⁵ Overall, 77% of the vildagliptin dose is excreted renally (22% as parent, 55% as primary metabolite). In the plasma, vildagliptin shows low (10%), reversible protein binding.⁷⁶ In patients in early stages of

nephropathy, vildagliptin significantly decreased albumin concentrations.⁸⁶

In a PK study, patients with stages 2–5 CKD, systemic exposure to vildagliptin was increased (C_{max} : 8%–66%; AUC extrapolated to infinity: 32%–134%) compared with healthy individuals.⁷⁸ Changes in exposure to vildagliptin showed no relationship with severity of CKD. No safety data were reported.⁷⁸ A later study showed that the mean AUC of vildagliptin after 14 days in patients with stages 2–4 CKD increased by 40%–100%. Vildagliptin C_{max} increased by 32%–37%.⁷⁹ Vildagliptin was generally safe and well tolerated in both healthy individuals and patients with different stages of CKD.

In treatment, no dose adjustment of vildagliptin is required in patients with stage 2 CKD. In patients with stages 3–5 CKD, for safety, the recommended dose is 50 mg od.⁵⁷

Saxagliptin

Saxagliptin is metabolized in the liver, producing an active metabolite. It is eliminated via the kidney (12%–29% as parent, 21%–52% as metabolite).⁷⁶ In the plasma, saxagliptin shows negligible protein binding.⁷⁶

The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial confirmed that the CV safety of saxagliptin met US Food and

Table 5 DPP-IV inhibitors: modes of action, modes of excretion, and studies investigating PK

Licensed drug	Mode of action	Mode of excretion	Study design	PK findings	Safety
Sitagliptin	<ul style="list-style-type: none"> Blocks DPP-IV, which degrades incretins⁷⁰ Facilitates GLP-1-mediated insulin secretion⁷⁰ 	<ul style="list-style-type: none"> 80% excreted renally⁷⁶ Clearance: 350 mL/min⁵⁶ 	<ul style="list-style-type: none"> Bergman et al (2007)⁷⁷ Open-label, two-part study Single 50 mg dose n=30 (normal RF, CKD 2, CKD 3, CKD 4, and CKD 5)^a Healthy individuals (n=145) from eleven other studies were included as a historical control group 	<ul style="list-style-type: none"> Compared with healthy individuals, AUC levels in patients with stages 2, 3, 4, and 5 CKD were elevated by factors of 1.6, 2.3, 3.8, and 4.5, respectively Compared with healthy individuals, C_{max} values in patients with stages 2, 3, 4, and 5 CKD were elevated by 1.4, 1.4, 1.8, and 1.4, respectively C_{24} increased as CKD increased t_{max} was significantly increased in patients with stage 5 CKD and the $t_{1/2}$ increased with increasing CKD 	Safety data not described
Vildagliptin	<ul style="list-style-type: none"> Blocks DPP-IV, which degrades incretins⁷⁰ Facilitates GLP-1-mediated insulin secretion⁷⁰ 	<ul style="list-style-type: none"> 77% of the vildagliptin dose is excreted renally⁷⁶ Clearance: 13 L/h⁵⁷ 	<ul style="list-style-type: none"> He et al (2007)⁷⁸ Design not specified Single 100 mg dose n=30 (normal RF, CKD 2, CKD 3, CKD 4, and CKD 5)^a 	<ul style="list-style-type: none"> Compared with individuals with normal RF, exposure to vildagliptin was increased in patients with stages 2, 3, 4, and 5 CKD (C_{max}: 8%–66%; AUC_{0–∞}: 32%–134%), in comparison with healthy individuals Reduction of CL_R was observed in patients with CKD, correlating with the GFR Differences in exposure did not correlate with the severity of CKD 	Safety data not described
Saxagliptin	<ul style="list-style-type: none"> Blocks DPP-IV, which degrades incretins⁷⁰ Facilitates GLP-1-mediated insulin secretion⁷⁰ 	<ul style="list-style-type: none"> Renal route (12%–29% as parent, 21%–52% as metabolite)⁷⁶ Clearance: ≈230 mL/min⁵⁸ 	<ul style="list-style-type: none"> He et al (2013)⁷⁹ Multicenter, open-label, parallel-group study 50 mg od for 14 days n=96 (normal RF, CKD 2, CKD 3, and CKD 4)^a Boulton et al (2011)⁸⁰ Open-label, parallel-group study Single 10 mg dose n=40 (normal RF, CKD 2, CKD 3, CKD 4, and CKD 5)^a 	<ul style="list-style-type: none"> Compared with individuals with normal RF, mean AUC after 14 days in patients with stages 2, 3, and 4 CKD increased by 40%, 71%, and 100%, respectively C_{max} showed increases of 37%, 32%, and 36%, respectively Compared with individuals with normal RF, saxagliptin AUC_{0–∞} values were 16%, 41%, and 108% higher in CKD patients with stages 2, 3, and 4, respectively As CrCl values decreased, the AUC values for saxagliptin (and its metabolite) either increased or became more variable 	<ul style="list-style-type: none"> Generally safe and well tolerated in both healthy individuals and patients with varying degrees of renal impairment No SAEs or clinically relevant changes in clinical laboratory tests, vital signs, or ECG findings were reported

Linagliptin	<ul style="list-style-type: none"> Blocks DPP-IV, which degrades incretins⁷⁰ Facilitates GLP-1-mediated insulin secretion⁷⁰ 	<ul style="list-style-type: none"> Enterohepatic system (>70%) and <6% renal⁷⁶ Clearance: 70 mL/min⁶⁹ 	<ul style="list-style-type: none"> Graefe-Moody et al (2011)⁸¹ Open-label, parallel-group study Single dose/multiple 5 mg dose n=51 CKD 2, CKD 3, and CKD 4 (with and without T2D), and CKD 5 (without T2D)⁸¹ Normal RF (with and without T2D) 	<ul style="list-style-type: none"> There was a trend toward slightly higher (20%–60%) linagliptin exposure in patients with renal impairment However, steady-state AUC and C_{max} values showed a large overlap and were not affected by the degree of CKD DPP-IV concentration at baseline showed no relationship with CKD severity 	<ul style="list-style-type: none"> No deaths and no SAEs occurred, and no AEs led to discontinuation of study medication During treatment, two patients (4%) reported AEs considered related to linagliptin by the investigator: one case of mild headache and one case of mild diarrhea and mild fatigue No other clinically significant AEs were observed
Alogliptin	<ul style="list-style-type: none"> Blocks DPP-IV, which degrades incretins⁷⁰ Facilitates GLP-1-mediated insulin secretion⁷⁰ 	<ul style="list-style-type: none"> Renal (>70% unchanged as parent)⁷⁶ Clearance: 170 mL/min⁶⁰ 	<ul style="list-style-type: none"> Karim et al (2008)⁸² Open-label study Single 50 mg dose n=48 (normal RF, CKD 2, CKD 3, CKD 4, CKD 5)⁸² 	<ul style="list-style-type: none"> Compared with healthy individuals, increases in alogliptin exposure were 1.7-, 2.1-, 3.2-, and 3.8-fold higher in patients with stages 2, 3, 4, and 5 CKD, respectively Mean C_{max} increased from 1.1- to 1.4-fold in renally impaired patients compared with healthy individuals Plasma exposure to the minor active metabolite was low in all patients Approximately 7.2% of the 50 mg dose was removed after 3 hours of dialysis in patients with stage 5 CKD Protein binding was ~20% for each group 	<ul style="list-style-type: none"> Safety data not described

Notes: *Study used criterion for degree of RI by CrCl: normal, >80 mL/min; CKD 2, 50–80 mL/min; CKD 3, 30–50 mL/min; CKD 4, <30 mL/min; CKD 5, ESRD. ^bStudy used same criterion as DPP-IV inhibitors, but used the CrCl range of 51–80 mL/min for CKD 2.

Abbreviations: AE, adverse event; AUC, area underneath the curve; AUC_{0–∞}, AUC extrapolated to infinity; C_{4h} , concentration at 24 hours; CKD, chronic kidney disease; CL_{cr} , clearance; C_{max} , maximum concentration; CrCl, creatinine clearance; DPP-IV, dipeptidyl peptidase-intravenous; ECG, electrocardiogram; ESRD, end-stage renal disease; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide-1; od, once daily; PK, pharmacokinetics; RF, renal function; RI, renal impairment; SAE, serious adverse event; $t_{1/2}$, half-life; t_{max} , time to reach maximum concentration; T2D, type 2 diabetes.

Drug Administration requirements.⁸⁷ Patients with no renal impairment or stage 2 CKD ($P < 0.0001$) and stages 3–4 CKD ($P = 0.041$) randomized to saxagliptin had greater improvement and less worsening of urine albumin-to-creatinine ratio (UACR) than patients randomized to placebo. Indeed, the relative risk of hospitalization for heart failure was comparable among patients with normal renal impairment or stage 2 CKD and patients with stages 3 and 4 CKD ($P = 0.43$).

One PK study showed that, compared with patients with normal renal function, saxagliptin AUC extrapolated to infinity values were 16%–108% increased in those with stages 2–4 CKD.⁸⁰ In addition, as CrCl values decreased, AUC values either increased or became more variable.

In treatment, no dose adjustment of saxagliptin is recommended for patients with stage 2 CKD,⁵⁸ however, to keep the plasma concentration comparable to individuals with normal renal function, the dose should be reduced to 2.5 mg od in patients with stages 3–4 CKD. However, saxagliptin is contraindicated in patients with stage 5 CKD requiring hemodialysis.⁵⁸

Linagliptin

Linagliptin is metabolized by the liver and does not have active metabolites. It is eliminated by the enterohepatic system (>70% unchanged as parent) and the kidney (<6%).⁷⁶ Linagliptin binds extensively to plasma proteins in a concentration-dependent manner and it has been calculated that, at the therapeutic dose (5 mg), most of the drug is protein-bound.⁷⁶ In a study in which linagliptin was administered to patients with T2D and renal dysfunction, there was a significant reduction in albuminuria.⁸⁸

In one PK study, although there was a trend toward slightly higher (20%–60%) linagliptin exposure in patients with CKD, steady-state AUC and C_{max} values showed a substantial overlap and were unaffected by the degree of CKD.⁸¹ No deaths or serious AEs occurred, and no AEs led to discontinuation. During treatment, two patients reported AEs considered related to linagliptin by the investigator. No other clinically significant AEs were observed.⁸¹

In treatment, in patients with CKD, no dose adjustment is required, and it can be administered across the CKD spectrum.⁵⁹

Alogliptin

Alogliptin is eliminated slowly, primarily via renal excretion (>70% unchanged as parent).⁷⁶ After oral administration, alogliptin is absorbed with 100% bioavailability and undergoes ~20% protein binding and limited hepatic metabolism.⁸⁹ In a

study by Sakata et al,⁹⁰ alogliptin reduced UACR following 12 weeks of treatment.

In a PK study involving patients with various degrees of renal impairment (not stated whether any patients had T2D), Karim et al⁸² determined that, compared with healthy individuals, increases in alogliptin exposure were 1.7–3.8-fold higher in patients with stages 2–5 CKD. The range of alogliptin AUC was comparable in healthy individuals and patients with stage 2 CKD. C_{max} increased from 1.1- to 1.4-fold in patients with CKD compared with healthy individuals. Plasma exposure suggested no accumulation of this metabolite in patients with increasing CKD. Approximately 7.2% of the 50 mg dose was eliminated after 3 hours of dialysis in patients with stage 5 CKD. Protein binding was ~20% for each CKD group.⁸²

In patients with stage 2 CKD (in the CrCl range >50 to ≤80 mL/min), no alogliptin dose adjustment is required. For patients with stage 3 CKD (in the CrCl range ≥30 to ≤50 mL/min), half of the recommended dose should be administered (12.5 mg od) to keep the plasma concentration comparable to healthy individuals.⁶⁰ Likewise, for patients with stages 4–5 CKD requiring dialysis, administration of a quarter of the recommended dose is advised (6.25 mg od).⁶⁰

Summary of DPP-IV inhibitor use in renal impairment

DPP-IV inhibitors can be used at all stages of CKD with dose reduction, except for linagliptin, which can be used without dose adjustment.^{56–60} A potential renoprotective effect (reduction in albuminuria) has been observed with all DPP-IV inhibitors.^{84,86–88,90} It is not clear whether this renoprotective effect is independent of changes in blood pressure and glycemic markers.

GLP-1 receptor agonists

GLP-1RAs function as incretin mimetics, which enhance the action of the endogenous incretin GLP-1, thereby controlling glycemia via several pathways, including enhancement of insulin secretion, inhibition of glucagon secretion, delay of gastric emptying, and induction of satiety.⁹¹ GLP-1RAs reduce HbA_{1c} by 0.55%–1.90%^{72,92} and have low rates of hypoglycemia,⁹³ with the advantage of promoting weight loss as well as controlling blood glucose.⁹¹ Owing to the effect of these agents on gastric emptying, AEs are typically gastrointestinal, that is, nausea and vomiting.⁹¹ However, gradually increasing the dose over a few weeks helps build a tolerance to such side effects. One possible, but infrequent, AE is pancreatitis.

Available evidence suggests that the rate of pancreatitis among patients using GLP-1RAs is low;⁹⁴ however, these data are not definitive and ongoing analysis is needed.⁹⁴

The short-acting compounds (short-lived receptor activation) consist of exenatide twice daily (bid) and lixisenatide od; the longer-acting compounds, which continuously activate receptors at their recommended dose, consist of liraglutide od and once weekly (ow) formulations of exenatide, albiglutide, and dulaglutide.⁹⁵ Exenatide⁹⁶ and liraglutide⁹⁷ have been shown to reduce albuminuria and proteinuria, respectively. A summary of the MOAs, elimination, PK, and safety of the GLP-1RAs is provided in Table 6.

Exenatide

Exenatide is a synthetic analog of exendin-4, which is extracted from the saliva of *Heloderma suspectum*.¹⁰³ Exenatide bid and ow are both eliminated mainly by glomerular filtration with subsequent proteolytic degradation. In addition, Zhang et al⁹⁶ reported decreased levels of 24-hour urinary albumin after 16 weeks of exenatide treatment ($P < 0.01$).

In a study by Linnebjerg et al,⁹⁸ exenatide (5 or 10 μg) was injected subcutaneously in 31 patients (including one patient with T2D) stratified by renal function (CrCl): normal and stages 2–5 CKD. PK data were then combined with four previous single-dose studies in patients with T2D to determine the relationship of exenatide clearance and CrCl. The half-life for patients with normal renal function and stages 2–5 CKD groups was 1.5–6.0 hours. After pooling data from several studies, least-squares geometric mean for exenatide clearance in individuals with normal renal function and patients with stages 2–4 CKD were 5.19–8.14 L/h.⁹⁸ Similar category and incidence of AEs were reported between the healthy and stages 2 and 5 CKD groups. No AEs were reported for the group with stage 3 CKD and no patients discontinued because of AEs.⁹⁸

No dose adjustment is required at stage 2 CKD to preserve therapeutic exposure. Dose adjustment is required in exenatide bid if CrCl in the patient is in the range 30–50 mL/min, which falls within the definition of stages 3a and 3b CKD;⁶¹ within the same CrCl range, exenatide ow is contraindicated.⁶² However, both exenatide bid and ow are contraindicated in patients with stages 4–5 CKD.^{61,62}

Lixisenatide

As with exenatide, lixisenatide is a synthetic version of exendin-4,¹⁰⁴ with resistance to physiological degradation by DPP-IV as a result of C-terminal modification.¹⁰⁴ Elimination occurs through glomerular filtration followed

by tubular reabsorption and subsequent metabolic degradation.⁷²

A study has shown that stage 2 CKD does not influence lixisenatide PK;⁶³ however, in patients with stages 3–4 CKD, the AUC was increased by 24%–46%.⁶³ In an open-label, nonrandomized, parallel-group study by Liu and Ruus,⁹⁹ no significant differences in AUC up to the last measurable concentration or C_{max} were observed for patients with stage 2 CKD compared with individuals with normal renal function or, indeed, for patients with stage 3 CKD versus normal function. However, in patients with stage 4 CKD, there was a significant increase in AUC up to the last measurable concentration, but not in C_{max} .⁹⁹ Treatment-emergent AEs were reported for one patient in each CKD group and four in the group of patients with normal renal function. AEs included headache (n=4; all with placebo), mild gastrointestinal disturbance (n=4), and mild muscle tightness (n=1).⁹⁹

No dose adjustment is required at stage 2 CKD to maintain therapeutic exposure. In treatment, monitoring is required with lixisenatide in patients whose CrCl is in the range 30–50 mL/min (which falls within the definition of stages 3a and 3b CKD).⁶³ Additionally, lixisenatide is contraindicated in patients with stages 4 and 5 CKD.⁶³

Liraglutide

Liraglutide has 97% sequence homology to GLP-1.⁶³ Liraglutide is endogenously metabolized in a similar process to large proteins with no specific organ established as a major route of elimination.⁶⁴ Zavattaro et al have shown a decrease in the proportion of patients with microalbuminuria; five patients in the study had microalbuminuria at baseline, but at 12 months, the levels in three of the patients had returned to normal ($P < 0.006$). Total microalbuminuria levels were improved in patients with normal renal function and stage 2 CKD ($P < 0.02$).¹⁰⁵ Investigating the superiority of liraglutide 1.8 mg versus placebo as an add-on to existing oral glucose-lowering agents with T2D and stage 3 CKD, the LIRA-RENAL study showed that liraglutide did not affect renal function and demonstrated better glycemic control (estimated treatment difference in HbA_{1c} from baseline was -0.66% [95% CI: -0.90 to -0.43 ; $P < 0.0001$]). Moreover, no difference in hypoglycemic AEs was reported between treatment groups; common AEs were gastrointestinal (liraglutide, 35.7%; placebo, 17.5%).¹⁰⁶

Jacobsen et al¹⁰⁰ investigated the effect of renal impairment on the PK of liraglutide in patients with T2D and normal renal function or stages 2–5 CKD. No defined relationship

Table 6 GLP- IRAs: modes of action, modes of excretion, and studies investigating PK

Licensed drug	Mode of action	Mode of excretion	Study design	PK	Safety
Exenatide	<ul style="list-style-type: none"> Enhancement of insulin secretion Inhibition of glucagon secretion Delay of gastric emptying and induction of satiety⁹¹ 	<ul style="list-style-type: none"> Mainly by glomerular filtration with proteolytic degradation⁶¹ Clearance: 9 L/h⁶¹ 	<ul style="list-style-type: none"> Linnebjerg et al (2007)⁹⁸ Open-label study Single sc injection of 5 or 10 µg n=31 (normal RF, CKD 2, CKD 3, and CKD 5)³ PK data were pooled with four previous single-dose studies in patients with T2D to explore the relationship of Clp/F with CrCl 	<ul style="list-style-type: none"> Mean exenatide $t_{1/2}$ values for patients with normal RF and stages 2, 3, and 5 CKD patients were 1.5, 2.1, 3.2, and 6.0 hours, respectively Corresponding total body CL/F rates for normal RF individuals and stages 2, 3, and 5 CKD were 8.14, 5.19, 7.11, and 1.30 L/h, respectively 	<ul style="list-style-type: none"> Category and frequency of AEs were comparable between the control (10 µg), CKD 2 (10 µg), and CKD 5 groups (5 µg) No AEs were observed for the group with CKD 3 (5 and 10 µg exenatide) No patients discontinued the study because of AEs
Lixisenatide	<ul style="list-style-type: none"> Enhancement of insulin secretion Inhibition of glucagon secretion Delay of gastric emptying and induction of satiety⁹¹ 	<ul style="list-style-type: none"> Elimination is mediated by glomerular filtration followed by tubular reabsorption and metabolic degradation⁷² Clearance: 35 L/h⁶³ 	<ul style="list-style-type: none"> Liu and Ruus (2009)⁹⁹ Open-label, nonrandomized, parallel-group study Single 5 µg sc dose n=32 (normal RF, CKD 2, CKD 3, and CKD 4)^b 	<ul style="list-style-type: none"> No significant differences in AUC_{0-24} or C_{max} were reported for patients with stage 2 CKD compared with individuals with normal RF (AUC_{0-24} ratio: 0.94; C_{max} ratio: 0.98), or for patients with stage 3 CKD compared with normal RF (AUC_{0-24} ratio: 1.28; C_{max} ratio: 0.99) In patients with stage 4 CKD, there was a significant increase in AUC_{0-24} but not in C_{max} (AUC_{0-24} ratio: 1.67; C_{max} ratio: 1.29) 	<ul style="list-style-type: none"> Treatment-emergent AEs were observed in one patient in each group with RI and four in the healthy group AEs included headache (n=4, all with placebo), mild GI disturbance (n=4), and mild muscle tightness (n=1)
Liraglutide	<ul style="list-style-type: none"> Enhancement of insulin secretion Inhibition of glucagon secretion Delay of gastric emptying and induction of satiety⁹¹ 	<ul style="list-style-type: none"> A similar process to large proteins without a specific organ as a major route of elimination⁶⁴ Clearance: 1.2 L/h⁶⁴ 	<ul style="list-style-type: none"> Jacobsen et al (2009)¹⁰⁰ Single-center, parallel-group, open-label study Single 0.75 µg sc dose n=30 Normal RF, CKD 2, CKD 3, CKD 4, and CKD 5^c Two patients with stage 3 CKD and one patient with CKD 5 had T2D 	<ul style="list-style-type: none"> Comparing individuals with normal RF with patients with CKD, exposure ratios were 0.67, 0.86, 0.73, and 0.74 in patients with stages 2, 3, 4, and 5 CKD, respectively No specific trend for change in PK parameters was evident across groups with increasing CKD, and renal CKD did not increase exposure to liraglutide 	<ul style="list-style-type: none"> Severity of CKD showed no relationship with an increased risk of AEs AEs were mild or moderate Nine patients (three healthy, one in each of the CKD 2 and CKD 3 groups, and two in each of the CKD 4 and CKD 5 groups) reported eleven AEs related to the GI system and established as probably/possibly related to liraglutide
Dulaglutide	<ul style="list-style-type: none"> Enhancement of insulin secretion Inhibition of glucagon secretion Delay of gastric emptying and induction of satiety⁹¹ 	<ul style="list-style-type: none"> Degradation into amino acids⁹² Clearance: at 0.75 and 1.5 mg doses, 0.111 and 0.107 L/h, respectively⁶⁶ 	<ul style="list-style-type: none"> Loghini et al (2014)¹⁰¹ Open-label study Single 1.5 mg dose n=48 (normal RF, CKD 2, CKD 3, CKD 4, and CKD 5)^d 	<ul style="list-style-type: none"> Dulaglutide AUC and C_{max} was <30% higher in patients with RI compared with individuals with normal RF There was no relationship between PK parameters and CKD based on eGFR There was no statistically significant linear relationship between exposure and CrCl A statistically significant but weak linear relationship was observed between CrCl and dulaglutide CL/F 	<ul style="list-style-type: none"> No notable differences in safety profiles between patients with RI and healthy individuals

Albiglutide	<ul style="list-style-type: none"> Enhancement of insulin secretion Inhibition of glucagon secretion Delay of gastric emptying and induction of satiety⁹¹ 	<ul style="list-style-type: none"> Degradation into amino acids⁶⁵ Clearance: 67 mL/h⁶⁵ 	<ul style="list-style-type: none"> Young et al (2014)⁹² Nonrandomized, open-label study Single 30 mg dose n=41 Normal RF, CKD 3, CKD 4, and CKD 5⁶ Also, a pooled analysis of four Phase III, randomized, double-blind (one open-label) studies: <ul style="list-style-type: none"> 30–50 mg dose n=1113 Normal RF, CKD 2, CKD 3, and CKD 4 	<ul style="list-style-type: none"> Relative to individuals with normal RF, single-dose AUC ratios were 1.32, 1.39, and 0.99 for patients with stages 3, 4, and 5 CKD, respectively Relative to individuals with normal RF, single-dose C_{max} ratios were 1.21, 1.23, and 1.11 for patients with stages 3, 4, and 5 CKD, respectively In the pooled analysis, there was a trend for increased glycemic lowering as CKD severity increased 	<ul style="list-style-type: none"> From the pooled analysis: <ul style="list-style-type: none"> Overall, nonserious AEs were reported at a comparable rate between the normal RF individuals and the stages 2–3 CKD groups; in contrast, the stage 4 CKD group demonstrated comparatively lower rates The SAEs showed a trend upward from the normal RF to the stage 3 CKD patients; but the stage 4 CKD group reported no SAEs Withdrawal incidence due to AEs was generally low but higher in the groups with RI
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Notes: ⁵Study used criterion for degree of RI by CrCl: normal, >80 mL/min; CKD 2, 51–80 mL/min; CKD 3, 31–50 mL/min; CKD 4, 31–50 mL/min; CKD 5, ESRD. ⁶Study used criterion for degree of RI by CrCl: normal, >80 mL/min; CKD 2, >50 and ≤80 mL/min; CKD 3, >30 and ≤50 mL/min; CKD 4, ≤30 mL/min; CKD 5, ESRD. ⁹¹Criterion used for degree of RI not specified. ⁹²Study used criterion for degree of RI by eGFR: normal, ≥90 mL/min/1.73 m²; CKD 2, ≥60 and <90 mL/min/1.73 m²; CKD 3, ≥30 and <60 mL/min/1.73 m²; CKD 4, ≥15 and <30 mL/min/1.73 m²; CKD 5, ESRD.

Abbreviations: AE, adverse event; AUC, area under the curve; AUC_{last}, AUC up to the last measurable concentration; CKD, chronic kidney disease; CL/F, apparent clearance; CLp/F, exenatide clearance; C_{max}, maximum concentration; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GI, gastrointestinal; GLP-1 RA, glucagon-like peptide-1 receptor agonist; PK, pharmacokinetics; RF, renal function; RI, renal impairment; SAE, serious adverse event; sc, subcutaneous; t_{1/2}, half-life; T2D, type 2 diabetes.

for change in PK parameters was evident across groups with increasing severity of CKD, and CKD did not increase exposure to liraglutide. Headache and gastrointestinal symptoms were the most commonly reported AEs. Reported AEs were mild to moderate in severity.¹⁰⁰

In treatment, no dose adjustment is necessary for patients with stages 2–3 CKD. As there is no therapeutic knowledge in patients with stages 4–5 CKD, liraglutide is contraindicated for use in patients with these diagnoses.⁶⁴

Dulaglutide

Dulaglutide has 90% sequence homology to GLP-1,⁹² with the GLP-1 portion of the molecule fused to an immunoglobulin 4 molecule, limiting renal clearance.⁹² Elimination occurs through degradation into amino acids.⁹²

Loghin et al¹⁰¹ assessed the PK of dulaglutide 1.5 mg in renal impairment compared to healthy individuals. The study included stages 2–5 CKD populations. There was no correlation between PK parameters and renal function based on eGFR. Also, there was no statistically significant correlation between exposure and CrCl. A weak, statistically significant linear correlation was established between CrCl and dulaglutide clearance. There were no prominent differences in safety profiles between patients with CKD and healthy individuals.¹⁰¹

In treatment, no dose adjustment of dulaglutide is necessary in patients with stages 2–3 CKD, but there is still limited experience in patients with stages 4–5 CKD; consequently, dulaglutide is contraindicated in these populations.⁶⁶

Albiglutide

Albiglutide shares 95% sequence homology with native GLP-1.¹⁰⁷ It is composed of a GLP-1 dimer fused to an albumin molecule.¹⁰⁸ The expected metabolic pathway for albiglutide is degradation to small peptides and individual amino acids by ubiquitous proteolytic enzymes.⁶⁵

In their investigation of the PK of albiglutide in patients with T2D stages 2–5 CKD groups, Young et al¹⁰² determined modest increases in plasma albiglutide concentration with increased severity of renal impairment and a trend for greater glycemic reductions as eGFR decreased, indicating no need for a dose adjustment. Overall, the incidences of nonserious AEs were comparable in the normal, and stages 2 and 3 CKD groups, whereas the stage 4 CKD group demonstrated lower rates. The serious AEs increased with increasing renal dysfunction up to stage 3 CKD, but the stage 4 CKD group reported no serious AEs.¹⁰²

In treatment, no dose adjustment of albiglutide is required for patients with stages 2–3 CKD. There is limited experience in patients with stages 4–5 CKD, and, therefore, albiglutide is contraindicated in these patients.⁶⁵

Summary of GLP-1RA use in renal impairment

Dose adjustment is required in exenatide bid in patients whose CrCl is in the range 30–50 mL/min, which falls within the definition of stages 3a and 3b CKD;^{56,61} within the same CrCl range, exenatide ow is contraindicated.⁶² Also, within the same range, monitoring is necessary when dosing lixisenatide.⁶³ By contrast, no dose alteration is necessary for liraglutide, albiglutide, and dulaglutide in stages 2, 3a, and 3b CKD.^{64–66} All GLP-1RAs are currently contraindicated in stages 4–5 CKD.^{61–66}

SGLT-2 inhibitors

SGLT-2 inhibitors inhibit glucose reabsorption and induce excretion of glucose in the urine.¹⁰⁹ Treatment with SGLT-2 inhibitors is associated with reductions in HbA_{1c} levels of 0.4%–1.5% and weight of up to 4.7 kg.^{110,111}

SGLT-2 inhibitors carry a low risk of hypoglycemia, unless combined with sulfonyleureas or insulin.¹¹² AEs include urinary and genital tract infections (which are usually not severe), especially in female patients.¹¹² SGLT-2 inhibitors appear to be associated with a small increased risk of euglycemic diabetic ketoacidosis and ketosis.^{112,113}

As their efficacy is reliant on renal function, SGLT-2 inhibitors are generally contraindicated in patients with eGFR <60 mL/min/1.73 m², mainly because of reduced efficacy.⁷² A summary of their MOAs, elimination, PK, and safety is provided in Table 7.

Dapagliflozin

Dapagliflozin is metabolized in both the kidney and the liver, with active metabolites generated at doses of >50 mg.¹¹⁹ It is primarily eliminated via the renal pathway.⁶⁷

Assessment of PK by Kasichayanula et al¹¹⁴ in healthy individuals and patients with T2D with normal renal function and stages 2–4 CKD showed that dapagliflozin plasma concentrations and its inactive metabolite dapagliflozin 3-*O*-glucuronide increased with increasing CKD severity. Steady-state C_{max} values for dapagliflozin were 4%–9% higher, and for dapagliflozin 3-*O*-glucuronide were 20%–52% higher in T2D patients with stages 2–4 CKD, compared with patients with T2D and normal renal function.¹¹⁴ Steady-state renal glucose clearance was reduced by

42%–84% in patients with stages 2–4 CKD, thereby also reducing its efficacy.¹¹⁴

In treatment, dapagliflozin is not recommended for use in patients with stages 3–5 CKD.⁶⁷ However, no dosage adjustment is suggested in patients with stage 2 CKD.

Canagliflozin

Canagliflozin is primarily metabolized by *O*-glucuronidation.¹¹⁶ It is eliminated largely unchanged in the feces (41.5%) and as metabolites in the urine (30.5%). Recent clinical data suggest that, in addition to the renal mechanism of action, a nonrenal mechanism partially contributes to glucose lowering for canagliflozin 300 mg but not 150 mg.¹¹⁵ Data from a substudy of the CANagliflozin cardiovascular Assessment Study (CANVAS) showed that 100 and 300 mg doses of canagliflozin significantly reduced the primary outcome of HbA_{1c} levels relative to placebo at week 18 (both *P*<0.001).¹²⁰

A study examining the impact of CKD on the PK and PD of canagliflozin 100 and 200 mg in Japanese patients with T2D found no significant effect of stage 3 CKD on the C_{max} of either canagliflozin dose.¹²¹ The canagliflozin AUC values were higher in patients with stage 3 CKD than in patients with T2D and normal renal function or stage 2 CKD. Changes from baseline in 24-hour urinary glucose excretion increased after administration but, in patients with stage 3 CKD, the increases were ~70% of those in patients with stage 2 CKD or normal.

In treatment, in patients with stage 2 CKD, no dose adjustment is needed.⁶⁸ Canagliflozin should not be initiated in patients with eGFR <60 mL/min/1.73 m², but in patients tolerating canagliflozin whose eGFR falls continuously below 60 mL/min/1.73 m², the dose of canagliflozin should be reduced to or managed at 100 mg od. Canagliflozin is contraindicated in patients with stages 3b–5 CKD, and in patients undertaking dialysis.

Empagliflozin

Empagliflozin is metabolized by glucuronidation without generation of active metabolites and eliminated in feces (41%) and urine (54%).⁶⁹

In a study comparing patients with normal renal function (and T2D), stage 2 CKD (and T2D), stage 3 CKD (and T2D), stage 4 CKD (four patients with T2D and four without), and stage 5 CKD (without T2D), Macha et al¹¹⁸ showed that the C_{max} for empagliflozin was similar for stages 3 and 5 CKD and with normal renal function (and T2D). However, empagliflozin C_{max} values were ~20% higher for patients with stages 2 and 4 CKD than for patients with normal renal function.¹¹⁸

Table 7 SGLT-2 inhibitors: modes of action, modes of excretion, and studies investigating PK and PD

Licensed drug	Mode of action	Mode of excretion	Study design	PK	PD	Safety
Dapagliflozin	Inhibition of SGLT-2, a high-capacity and low-affinity glucose transporter, expressed in the luminal membranes of the proximal renal tubules ¹⁰⁹	<ul style="list-style-type: none"> Primarily renal⁶⁷ Clearance: 207 mL/min⁶⁷ 	<ul style="list-style-type: none"> Kasichayanula et al (2013)¹¹⁴ Open-label, parallel-group study Single 50 mg dose n=40 T2D patients with normal RF, CKD 2, CKD 3, and CKD 4 with T2D³ Healthy individuals Patients with T2D received multiple doses of dapagliflozin 20 mg od for evaluation of steady-state PK and PD 	<ul style="list-style-type: none"> Steady-state C_{max} values for dapagliflozin were 4%, 6%, and 9% higher, and for D30G were 20%, 37%, and 52% higher in T2D patients with stages 2, 3, and 4 CKD, respectively, versus T2D patients with normal RF 	<ul style="list-style-type: none"> Reduced steady-state renal glucose clearance by 42%, 83%, and 84% in patients with stages 2, 3, and 4 CKD, respectively 	<ul style="list-style-type: none"> 35% of participants experienced AEs, which were all mild or moderate in intensity No SAEs No trend in the frequency of AEs in relation to the degree of kidney function
Canagliflozin	Inhibition of SGLT-2, a high-capacity and low-affinity glucose transporter, expressed in the luminal membranes of the proximal renal tubules ¹⁰⁹	<ul style="list-style-type: none"> In the feces (41.5%) and as metabolites in the urine (30.5%)¹¹⁶ Clearance: 192 mL/min⁶⁸ 	<ul style="list-style-type: none"> Inagaki et al (2014)^{b,117} Open-label, randomized, two-way crossover study Single 100 and 200 mg dose n=24 T2D patients with normal RF or CKD 2 and CKD 3 	<ul style="list-style-type: none"> No significant effect in those with CKD 3 on C_{max} AUC was greater in those with CKD 3 than in those without, after both canagliflozin doses 	<ul style="list-style-type: none"> Urinary glucose excretion increased after administration of both doses In patients with CKD 3, the increase was ~70% of that in patients with normal RF or CKD 2 	<ul style="list-style-type: none"> No AEs leading to study discontinuation, deaths, other SAEs, or other significant AEs Incidence of AEs was not affected by degree of CKD or canagliflozin dose None of the patients developed hypoglycemia
Empagliflozin	Inhibition of SGLT-2, a high-capacity and low-affinity glucose transporter, expressed in the luminal membranes of the proximal renal tubules ¹⁰⁹	<ul style="list-style-type: none"> In feces (41%) and urine (54%)⁶⁹ Clearance: 10.6 L/hour⁶⁹ 	<ul style="list-style-type: none"> Macha et al (2014)^{c,118} Open-label study Single 50 mg dose n=40 T2D patients with normal RF Non-T2D patients and T2D patients with CKD 2, CKD 3, CKD 4, and CKD 5^b 	<ul style="list-style-type: none"> $AUC_{0-\infty}$ values increased by ~18%, 20%, 66%, and 48% in patients with stages 2, 3, 4, and 5 CKD, respectively, in comparison with healthy individuals C_{max} for empagliflozin was similar for stages 3 and 5 CKD versus patients with T2D and normal RF C_{max} values were ~20% higher for patients with stages 2 and 4 CKD than for patients with T2D and normal RF 	<ul style="list-style-type: none"> Urinary glucose excretion decreased with increasing CKD severity and correlated with decreased eGFR and Cl_{CR} 	<ul style="list-style-type: none"> Six treatment-emergent AEs were reported by four patients; all were mild in intensity AEs were considered drug-related by the investigator in two patients: erythema and pruritus in a patient with stage 3 CKD and pruritus in a patient with stage 5 CKD AEs resolved without treatment by the end of the study No effects on safety laboratory values, vital signs, or ECG parameters were observed

Notes: ^aStudy used criterion for degree of RI by CrCl: normal >80 mL/min; CKD 2, 51–80 mL/min; CKD 3, 30–50 mL/min; CKD 4, <30 mL/min; CKD 5, ESRD. ^bStudy used criterion for degree of RI by CrCl: normal or CKD 2, eGFR ≥ 80 mL/min/1.73 m²; CKD 3, eGFR ≥ 30 and <50 mL/min/1.73 m²; ^cStudy used criterion for degree of RI by eGFR: normal, ≥ 90 mL/min/1.73 m²; CKD 2, 60–89 mL/min/1.73 m²; CKD 3, 30–59 mL/min/1.73 m²; CKD 4, <30 mL/min/1.73 m²; CKD 5, ESRD.

Abbreviations: AE, adverse event; AUC, area under the curve; $AUC_{0-\infty}$, AUC extrapolated to infinity; CKD, chronic kidney disease; Cl_{CR} , maximum concentration; D30G, dapagliflozin 3-O-glucuronide; eGFR, estimated glomerular filtration rate; ECG, electrocardiogram; ESRD, end-stage renal disease; od, once daily; PD, pharmacodynamics; PK, pharmacokinetics; RF, renal function; RI, renal impairment; SAE, serious adverse event; SGLT-2, sodium-glucose cotransporter-2; T2D, type 2 diabetes.

In treatment, no dose adjustment of empagliflozin is necessary for patients with stage 2 CKD, but empagliflozin treatment should not be administered in patients with eGFR <60 mL/min/1.73 m². In patients tolerating empagliflozin whose eGFR falls continuously beneath 60 mL/min/1.73 m², the dose of empagliflozin should be altered or managed at 10 mg od and stopped when eGFR is continuously beneath 45 mL/min/1.73 m². Empagliflozin is contraindicated in patients with stages 3b to 5 CKD.⁶⁹

SGLT-2 effect on proteinuria

Many studies have shown evidence of renoprotection with use of SGLT-2 inhibitors in patients with CKD.^{120,122–124} SGLT-2 inhibition may mediate their renoprotective effects by decreasing intra-glomerular pressure.¹²⁵ Indeed, inhibition of SGLT-2 can normalize the NaCl concentration at the macula densa and lower glomerular hyperfiltration, thereby lowering glomerular hyperfiltration and albuminuria.¹²⁵ This MOA could explain the reduction of albuminuria with SGLT-2 (dapagliflozin, canagliflozin, and empagliflozin) treatment described in clinical studies.^{120,122–124}

In a study by Kohan et al,¹²² UACR values of >1,800 mg/g during the 104-week treatment period were reported in a higher percentage of patients receiving placebo (13.3%) than patients receiving dapagliflozin 5 (10.8%) or 10 mg (9.5%), indicating decreased albuminuria with dapagliflozin. In Phase III studies, canagliflozin treatment was also associated with decreased albuminuria and an early decrease in eGFR.^{120,124} Yale et al¹²⁴ determined a lower proportion of subjects in the canagliflozin 100 and 300 mg groups progressing from normoalbuminuria to micro- or macroalbuminuria, or from micro- to macroalbuminuria compared to those in the placebo group (5.1%, 8.3%, and 11.8%, respectively); likewise, the CANVAS substudy reported decreases in UACR from baseline at canagliflozin 100 mg (−9.6, 95% CI: −13.0 to −6.1) and 300 mg doses (−9.5, 95% CI: −12.9 to −6.1).¹²⁰

In the Efficacy and Safety of Empagliflozin (BI 10773) in Patients With Type 2 Diabetes and Renal Impairment (EMPA-REG RENAL) placebo-controlled trial, small decreases in eGFR and albuminuria were shown in empagliflozin-treated T2D patients with stages 2–3 CKD.¹²³ UACR was enhanced with empagliflozin (10 and 25 mg) after 52 weeks in patients with stage 2 CKD (empagliflozin 10 mg placebo adjusted mean difference: −184.59, *P*=0.0831; at 25 mg: −235.86, *P*=0.0257) and stage 3 CKD (empagliflozin 25 mg placebo adjusted mean difference: −183.78, *P*=0.0031). Moreover, greater proportions of patients with stage 3 CKD shifted from macroalbuminuria at baseline to microalbuminuria, or from microalbuminuria to no albuminuria with empagliflozin

compared to placebo (32.6% vs 8.6% and 27.5% vs 21.4%, respectively).

Summary of SGLT-2 inhibitor use in renal impairment

For patients with stage 3 CKD or greater, SGLT-2 inhibitors (dapagliflozin, canagliflozin, and empagliflozin) either require dose adjustment or are contraindicated.^{67–69} However, a renoprotective effect has been observed with all SGLT-2 inhibitors.^{120,122–124}

Impact of CKD on treatment algorithm

Leading on to the impact of CKD on the T2D treatment algorithm, examples of the dose maintenance and withdrawal of glucose-lowering therapies in the American Diabetes Association/European Association for the Study of Diabetes 2015 guidelines are described in Figure 1.

Ongoing or data pending studies

Clinical investigations of DPP-IV inhibitor, GLP-1RA, and SGLT-2 inhibitor therapies in renal impairment or protection are being carried out in several ongoing studies. A summary is provided in Table 8.

Incretin-based therapies

The Differential Effects of Diabetes Therapy on Inflammation study aims to determine whether different diabetes treatments have different effects on inflammation, particularly in the kidney, and includes¹²⁶ patients who need additional glycemic therapy and who are prescribed a DPP-IV inhibitor, GLP-1RA, or insulin.¹²⁶

Given the relationship between CV safety and T2D and the uncertainty surrounding the CV risk of some therapies, the Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients With Type 2 Diabetes Mellitus (CARMELINA) will compare the CV and renal safety of linagliptin versus placebo, when added to standard care in ~8,000 patients with T2D at high CV risk.¹²⁷ Clinical data have previously shown that linagliptin reduces albuminuria.^{88,140} The Efficacy, Safety and Modification of Albuminuria in Type 2 Diabetes Subjects with Renal Disease with Linagliptin (MARLINA) study will investigate this renoprotective effect.¹²⁸ The Renal Effects of DPP-IV Inhibitor Linagliptin in Type 2 Diabetes (RENALIS) study will further investigate this drug's action on renal physiology.¹²⁹ In addition, delayed elimination of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) in renal insufficiency may influence the PK and PD of linagliptin;¹⁴¹ consequently, another study will investigate the effects of linagliptin on active

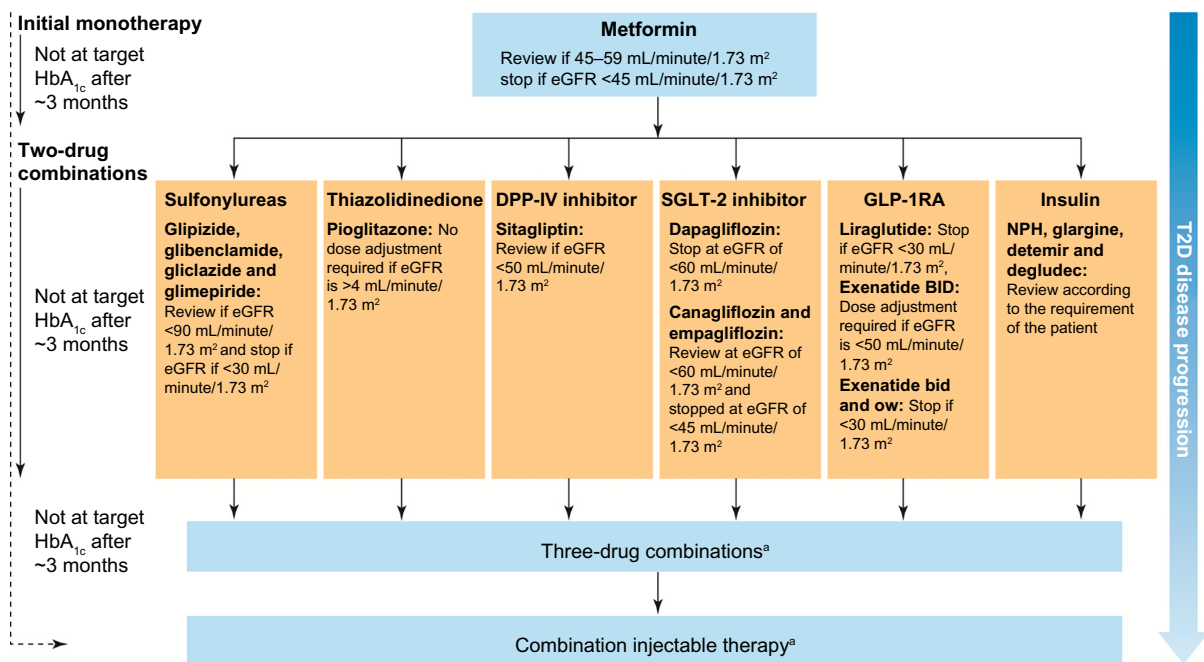


Figure 1 The effect of CKD in the European Association for the Study of Diabetes/American Diabetes Association (EASD/ADA) treatment algorithm.

Note: ^aDrugs are subject to the same dose reductions in CKD as in the initial monotherapy and two-drug combination examples.

Abbreviations: bid, twice daily; CKD, chronic kidney disease; DPP-IV, dipeptidyl peptidase-IV; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated hemoglobin; NPH, neutral protamine Hagedorn; ow, once weekly; SGLT-2, sodium-glucose cotransporter-2.

GLP-1 concentrations in patients with renal impairment.¹³⁰ Examining the safety of a DPP-IV inhibitor in a real-world setting, a postmarketing study will compare the rates of hospitalization for acute kidney injury among patients with T2D who are new initiators of saxagliptin and those patients who are new initiators of other T2D therapies.¹³¹

Several studies are currently examining the safety and renoprotective effects of GLP-1RAs. Cardiorenal syndrome type IV is impaired cardiac function due to CKD and is characterized by ventricular hypertrophy, diastolic dysfunction, and/or increased risk of CV AEs.¹⁴² The Extended Release Exenatide versus Placebo in Diabetic Patients with Type IV Cardiorenal Syndrome study is evaluating the quantitative impact of 38 weeks of treatment on cardiac biomarkers in patients at high risk of developing cardiorenal syndrome type IV.¹³² Additionally, the mechanistic and clinical effects of lixisenatide on renal physiology and biomarkers in T2D patients are being explored in the Effect of LIXIsenatide on the Renal System (ELIXIRS) study.¹³³ Meanwhile, the effect of liraglutide on CKD and kidney function in diabetes is being assessed in the Effect of Glucagon-like-peptide 1 (GLP-1) Receptor Agonism on Diabetic Kidney Disease study.¹³⁴ Dulaglutide has been shown to have similar efficacy and safety to other agents in its class and provide better glycemic control than placebo,⁹² but there is little experience with its use in populations with renal impairment. The AWARD-7

study will provide important information in this regard by comparing the efficacy and safety of dulaglutide with insulin glargine on glycemic control in patients with T2D and stages 3–4 CKD.¹³⁵

SGLT-2 inhibitors

Glycemic control and renal safety are being investigated in the Effect of Dapagliflozin on Blood Glucose Level and Renal Safety in Patients With Type 2 Diabetes study.¹³⁶ In Phase III studies, canagliflozin treatment was also associated with decreased albuminuria and an early decrease in eGFR;^{120,124} the Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE) trial is a randomized, double-blind, placebo-controlled trial intended to assess whether canagliflozin can delay the development of diabetic nephropathy.¹³⁸ The renoprotective effect of canagliflozin relative to placebo will be assessed by the composite endpoint of reduction in progression to stage 5 CKD, doubling of serum creatinine, and renal or CV death. Further assessing CV risk, the Effects of Canagliflozin on Renal Endpoints in Adult Participants with Type 2 Diabetes Mellitus (CANVAS-R) study will recruit 5,875 individuals with T2D.¹³⁷

The EMPA-REG RENAL trial showed that albuminuria decreased in T2D patients with stages 2–3 CKD treated with empagliflozin.¹²³ To further investigate the impact of empagliflozin on renal kinetics, The Effect of Empagliflozin

Table 8 Ongoing or data pending studies

Drug class	Ongoing study or results pending	ClinicalTrials.gov identifier	Completion date
Incretin-based therapies	The Differential Effects of Diabetes Therapy on Inflammation ¹²⁶	NCT02150707	August 2015 (no data presented)
	Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus (CARMELINA) ¹²⁷	NCT01897532	January 2018
	Efficacy, Safety and Modification of Albuminuria in Type 2 Diabetes Subjects With Renal Disease With Linagliptin (MARLINA-T2D) ¹²⁸	NCT01792518	December 2015
	Renal Effects of DPP-4 Inhibitor Linagliptin in Type 2 Diabetes (RENALIS) ¹²⁹	NCT02106104	May 2016
	Effects of Linagliptin on Active GLP-I Concentrations in Subjects With Renal Impairment ¹³⁰	NCT01903070	January 2016
	Risk of Acute Kidney Injury Among Patients With Type 2 Diabetes Exposed to Oral Antidiabetic Treatments ¹³¹	NCT01377935	November 2015 (no data presented)
	Extended Release Exenatide versus Placebo in Diabetic Patients with Type 4 Cardiorenal Syndrome (EXTEND-CRS) ¹³²	NCT02251431	February 2017
	Effect of Lixisenatide on the Renal System (ELIXIRS) ¹³³	NCT02276196	February 2016
	The Effect of Glucagon-like-peptide I (GLP-I) Receptor Agonism on Diabetic Kidney Disease ¹³⁴	NCT01847313	November 2015
	A Study Comparing Dulaglutide With Insulin Glargine on Glycemic Control in Participants With Type 2 Diabetes (T2D) and Moderate or Severe Chronic Kidney Disease (CKD) (AWARD-7) ¹³⁵	NCT01621178	November 2016
SGLT-2 therapies	A Study to Evaluate the Effect of Dapagliflozin on Blood Glucose Level and Renal Safety in Patients With Type 2 Diabetes (DERIVE) ¹³⁶	NCT02413398	February 2017
	A Study of the Effects of Canagliflozin (JNJ-28431754) on Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus (CANVAS-R) ¹³⁷	NCT01989754	January 2017
	Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE) ¹³⁸	NCT02065791	January 2020
	Effect of Empagliflozin Kinetics on Renal Glucose Reabsorption in Patients With Type II Diabetes and Healthy Controls ¹³⁹	NCT01867307	October 2015 (no data presented)

Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-I, glucagon-like peptide-1; SGLT-2, sodium-glucose cotransporter-2.

Kinetics on Renal Glucose Reabsorption in Patients with Type II Diabetes and Healthy Controls study, which has no current published data, investigated the change from baseline of renal tubular maximum reabsorptive capacity for glucose at end of empagliflozin treatment.¹³⁹

Conclusion

Improved blood glucose control through pharmacological intervention can reduce the incidence and progression of CKD.^{8,13,14} CKD is a common complication of T2D and should inform the choice of initial and subsequent drug therapy based on individualized glycemic targets.

Apart from the thiazolidinedione pioglitazone,²⁰ which can be used across the spectrum of CKD, there are contraindications and dose adjustments required for all the remaining conventional therapies, including metformin, sulfonylureas, meglitinides, and insulin.^{21–33} The inclusion of several newer therapy classes in treatment guidelines increases the likelihood that T2D will be well managed,¹⁷ with the attendant positive impact on the long-term incidence and progression of renal impairment.

Clinical studies suggest that reductions in albuminuria may be renoprotective and have been observed with all DPP-IV inhibitors,^{76,84,86,88,90} all SGLT-2 inhibitors, as demonstrated in the EMPA-REG study,^{120,122,123} and the GLP-1RAs liraglutide and exenatide.^{96,105} However, as with conventional therapies, not all of these newer therapies can be used when CKD is present, and some require dose adjustment with incident CKD.^{56–58,60–63,68,69} In contrast to other DPP-IV inhibitors,^{56–58,60} linagliptin can be used across the spectrum of CKD with no dose adjustment.⁵⁹ No dose adjustment is required for liraglutide, albiglutide, and dulaglutide in stages 2–3 CKD;^{64–66} however, they are all currently contraindicated in CKD stages 4–5.^{61–66} At CKD stages of 3 or more, the SGLT-2 inhibitors dapagliflozin, canagliflozin, and empagliflozin either require dose adjustment or are contraindicated.^{67–69}

Data from ongoing clinical trials with larger populations are awaited to further determine the safety and efficacy profile of DPP-4 inhibitors, GLP-1RAs, and SGLT-2 inhibitors in patients with T2D and CKD.^{126–139} Ongoing trials, such as CARMELINA, MARLINA, ELIXIRS, A Study Comparing

Dulaglutide With Insulin Glargine on Glycemic Control in Participants With Type 2 Diabetes (T2D) and Moderate or Severe Chronic Kidney Disease (CKD) (AWARD-7), CREDENCE, and CANVAS-R, in particular, will help to confirm the position of these new therapy classes in patients with CKD.

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Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

Professor Melanie Davies has acted as a consultant, advisory board member, and speaker for Novo Nordisk, Sanofi-Aventis, Eli Lilly, Merck Sharp and Dohme, Boehringer Ingelheim, AstraZeneca, and Janssen, and as a speaker for Mitsubishi Tanabe Pharma Corporation and Takeda. She has received grants in support of investigator-initiated trials from Novo Nordisk, Sanofi-Aventis, and Eli Lilly. Dr Sudesna Chatterjee has received speaker fees and educational funding from Janssen, Eli Lilly, Novo Nordisk, Astra Zeneca, and Boehringer Ingelheim. Professor Kamlesh Khunti has received funds for research and honoraria for speaking at meetings from, and served on advisory boards for, Astra Zeneca, Boehringer Ingelheim, Lilly, Novartis, Roche, Servier, Sanofi Aventis, MSD, Janssen, and Novo Nordisk. The authors report no other conflicts of interest in this work.

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