



Managing hyperglycaemia in patients with diabetes and diabetic nephropathy-chronic kidney disease

2018

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Evidence grades for the recommendations

The following evidence grading has been used to determine the strength of the recommendations; the suggested audit standards; and the questions for areas that require future research.

1A – Strong recommendation: high-quality evidence
1B – Strong recommendation: moderate-quality evidence
1C – Strong recommendation: low-quality evidence
1D – Strong recommendation: very low-quality evidence
2A – Weak recommendation: high-quality evidence
2B – Weak recommendation: moderate-quality evidence
2C – Weak recommendation: low-quality evidence
2D – Weak recommendation: very low-quality evidence

Search strategy

The recommendations are based on a systematic review of the Cochrane Library, PubMed/MEDLINE, Google Scholar and Embase, using the following key words: type 1 diabetes, insulin, chronic kidney disease, nephropathy, hypoglycaemia, insulin, sulfonylureas, metformin, SGLT-2 inhibitors, pioglitazone, DPP-4 inhibitors, GLP-1 analogues and meglitinides.

Review date: March 2020

1 Introduction: glycaemic targets in the prevention and management of diabetic nephropathy and chronic kidney disease

The management of diabetes is predicated on the basis of reducing hyperglycaemia to improve hyperglycaemic symptoms, with supportive evidence that this will prevent the onset, and slow down progression, of renal and vascular complications over time.

The precise level of glycaemic control that delivers benefit remains contentious because, inevitably, the individualised approach to care and the evidence base from different cohorts do not allow clear extrapolation. The glycaemic management of type 1 diabetes and type 2 diabetes and the respective renal benefits require separate consideration, which in part reflects the different evidence base and lifetime risks of complications, and the greater risk for hypoglycaemia that arises when several concurrent therapies are used alongside insulin as renal function deteriorates.

In addition, the risk–benefit equation of tighter glycaemic control for renal and vascular complications alters as nephropathy / chronic kidney disease (CKD) progresses.

Recent national clinical guidelines have not distinguished between glycaemic targets for those with or without diabetic nephropathy (DN)–CKD,^{1,2} and consensus groups have extrapolated from contemporary general recommendations, such as with Kidney Disease Outcomes Quality Initiative (KDOQI) in 2012, which suggested a target HbA1c level of 7% (53 mmol/mol) in those with CKD.³

By contrast, the more recent European Renal Best Practice (ERBP) guidance in 2015 recognised the lack of prospective randomised trials in CKD stage 3b or worse, and suggested ‘vigilant attempts to tighten glycaemic control when [HbA1c] values were >8.5% (69 mmol/mol)’ but recommended against tighter glycaemic control, given the hypoglycaemia risk.⁴

A retrospective observational case cohort study found that HbA1c levels of <6.5% (48 mmol/mol) and >8% (63 mmol/mol) were associated with increased mortality in patients with CKD stages 3–4.⁵

The most recent Cochrane collaborative meta-analysis from 2017 found that there were comparable risks of renal failure, death and major cardiovascular events among patients with stringent glycaemic control (HbA1c <7% (54 mmol/mol)), as opposed to those with less tight control, beyond small clinical benefits on the onset and progression of microalbuminuria.⁶

Type 1 diabetes

The Diabetes Control and Complications Trial / Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) studied adolescents and adults with type 1 diabetes who were intensively managed for a mean duration of 6.5 years to a target HbA1c of 6% (43 mmol/mol) (achieved 7.2% (55 mmol/mol)). The study clearly demonstrated a reduced incidence for the development and progression of microalbuminuria and macroalbuminuria in the primary and secondary prevention groups.⁷ Furthermore, ongoing surveillance for up to 18 years with less intensive glycaemic control (HbA1c subsequently maintained at a mean of 8% (63 mmol/mol)) revealed a legacy effect. That is, the intensive group continued to experience lower rates of incident microalbuminuria and macroalbuminuria but also had less progression to CKD (estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m²) and hypertension. At follow-up, however, the intensive group’s glycaemic control was indistinguishable from the control group.⁸

At trial entry, none of the subjects in DCCT had CKD (the GFR estimated from creatinine clearance (CrCl) averaged 128 mL/min in both the primary and secondary prevention

groups). Urinary albumin excretion was normal in the primary prevention group and was <140 µg/minute (mean 14 µg/minute) in the secondary prevention group.⁷

A recent country-wide, registry-based observational study from Sweden confirmed the recognised excess mortality from type 1 diabetes compared with the general population, even with mean updated HbA1c values of <52 mmol/mol. Increased HbA1c values remained a powerful risk factor for death after adjustment for renal complications, which indicates a residual risk associated with poor glycaemic control.

All-cause and cardiovascular mortality, however, in those with renal disease was virtually unchanged for patients with a time-updated HbA1c of 53–62 mmol/mol versus those with values of 52 mmol/mol or lower, which suggests that there is no additional benefit of tighter glycaemic control in those with type 1 diabetes who have renal disease.⁹ Thus it would be appropriate to reduce the development and progression of nephropathy via tight glycaemic control in younger patients (HbA1c target individualised to 48–58 mmol/mol), with a requirement to at least maintain moderate control (HbA1c of <63 mmol/mol) after a period of 10 years. There are, however, vascular benefits from tight glycaemic control (target HbA1c of 48–58 mmol/mol) over a longer period in younger patients with type 1 diabetes.

The current UK National Institute for Health and Care Excellence (NICE) guidance to aim for the even tighter target HbA1c of 48 mmol/mol utilises the DCCT target¹⁰ which, although rarely achieved in that study, reduced both the progression of microalbuminuria and normoalbuminuric progression to microalbuminuria. From intervention studies with type 1 diabetes patients who have DN-CKD, there is no current evidence that renal or other outcomes are improved by achieving an HbA1c of 48 mmol/mol.

While recognising that individualised care targets should apply, it may still be broadly reasonable to aim for an HbA1c of 58–62 mmol/mol in type 1 diabetes patients who have DN-CKD and/or CKD stages 3–4, unless values of 48–58 mmol/mol are achievable in younger patients (below the age of 40 years) who are on an intensive self-management regime with documented hypoglycaemia avoidance and an intensive insulin regime on continuous subcutaneous insulin infusion (CSII) or multiple doses of insulin therapy.

The Joint British Diabetes Societies (JBDS) guidelines for patients with diabetes of any sort who are on haemodialysis recommended HbA1c targets of 58–68 mmol/mol. This was based on U-shaped survival curves at values above and below this range and the inherent challenge of assessing glycaemic control in the context of related renal anaemia,¹¹ which is present in 18–27% of patients with CKD stage 3 and is even more prevalent in those with more advanced CKD.^{12,13} The basis for renal anaemia can affect the level of HbA1c, with the normochromic secondary anaemia leading to falsely lower HbA1c¹⁴ while iron deficiency artefactually elevates the HbA1c value.¹⁵

Type 2 diabetes

With the exception of younger patients who have type 2 diabetes (below the age of 40) where the lifetime renal–cardiovascular disease risk may justify similar glycaemic targets to those for patients with type 1 diabetes, the evidence base for intensive glycaemic control comes from several sources with broadly different trial design and outcomes.

The Steno-2 randomised trial was conducted in 80 patients with microalbuminuria, and reported at intervals over 21 years' follow-up, following a mean of 7.8 years of intensified glycaemic control as part of a package of multiple cardiovascular disease risk factor interventions and lifestyle modification. Although the target HbA1c was set at 48 mmol/mol, the mean HbA1c that was achieved in the study with an insulin-dominant regime was

63 mmol/mol. At various time points there was clear evidence that a reduced number of complications were evolving and developing, including cardiovascular and microvascular (including albuminuric) outcomes.^{16,17}

With respect to renal outcomes, in the Steno-2 randomised trial there was a 48% significant risk reduction in the progression to macroalbuminuria through multiple risk factor intervention. Although the sample size was small, there was also a borderline significant reduction in progression to end-stage renal disease (ESRD) ($p=0.06$).

One key message of the multiple risk factor approach was that, in keeping with other studies that demonstrated a legacy effect of early control, the continued benefits were apparent after a further 13-year follow-up, despite there being comparative HbA1c levels of 58 mmol/l and 59 mmol/l in the intensive and control groups at 21 years' follow-up.¹⁷

By contrast, the ACCORD study design (with a target HbA1c of 42 mmol/mol and a broadly based intensive insulin regime) found that, at the stage of CKD, intensive glycaemic control led to increased cardiovascular risk and no benefit in terms of the progression of renal disease.¹⁸

In patients who did not have CKD at trial entry, there was a delay in the onset of albuminuria but no reduction in their progress towards renal failure or the need for renal replacement therapy, and this was achieved at the cost of a high risk for severe hypoglycaemia and increased mortality.¹⁹

The ADVANCE study was a predominantly sulfonylurea-based study and it recorded that intensive glucose control to a target HbA1c of 6.5% (48 mmol/mol) reduced the development and progression of both albuminuric and glomerular filtration outcomes in patients with type 2 diabetes, although the number of events was low.²⁰ Over 5 years, the numbers needed to treat (NNT) to prevent one end-stage renal event ranged from 410 participants in the overall study to 41 participants with macroalbuminuria at baseline.^{20,21}

The longer-term, 6-year follow-up of the ADVANCE study found that, while blood pressure (BP) control delivered persistent albeit attenuated benefits in terms of mortality, there was no evidence that glycaemic control led to macrovascular or mortality benefits in the longer term.^{21,22}

Two recent meta-analyses demonstrated that, although intensive glucose control (target HbA1c 6.1–7.1% (43–54 mmol/mol)) can lead to a reduced incidence of the surrogate renal measures of microalbuminuria and macroalbuminuria in patients with type 2 diabetes, there was no significant impact on clinical renal outcomes such as a doubling of serum creatinine, progression to ESRD, death from renal disease or other complications.^{23,24} A more recent meta-analysis included data from the Veteran Affairs (VA) and UK Prospective Diabetes Study (UKPDS) studies to imply that intensive glycaemic control had benefits in reducing these hard renal outcomes, but the heterogeneity of glycaemic targets limits the validity of that conclusion.²⁵

Given these discrepancies, the Cochrane collaboration has recently initiated a review to examine the efficacy and safety of insulin and other pharmacological interventions for lowering blood glucose in patients with diabetes and CKD.²⁶

The JBDS has already reported and suggested an HbA1c of 58–68 mmol/mol in patients with diabetes who are on haemodialysis, given the hypoglycaemic and cardiovascular safety considerations and the inherent inaccuracy of HbA1c, with falsely lower values in those with anaemia in the context of CKD.¹¹

On balance, whereas the lifelong risk that hyperglycaemia will lead to the development and progression of DN-CKD (and other complications) requires a more intensive glycaemic-

lowering strategy in those with early onset type 2 diabetes diagnosed before the age of 40, options for intensive glycaemic control after that point with an insulin-intensive regime do not appear to be appropriate with HbA1c levels of <7% (53 mmol/mol).

The recent cardiovascular safety studies with non-insulin based therapies among cohorts of patients with established cardiovascular disease using empagliflozin and the daily and weekly glucagon-like peptide-1 (GLP-1) analogues included a cohort with established DN-CKD, and found that these patients had less evolution of albuminuria to evident proteinuria with an attained HbA1c of 7.3–7.6% (56–60 mmol/mol).

In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG) study group, with the sodium glucose co-transporter-2 (SGLT-2) inhibitor empagliflozin, virtually all had established cardiovascular disease at baseline and all had an eGFR of >30 mL/min/1.73 m². CKD stage 3a was present in 17.8% of participants and 7.7% of participants had CKD stage 3b. In addition, 28.7% had microalbuminuria and 11% had macroalbuminuria.²⁷ The cohort with a reduced eGFR had a baseline HbA1c of 8.1% (65 mmol/mol), which fell to 7.6% (60 mmol/mol) – only 0.3% (3 mmol/mol) lower than the placebo. Thus despite there being only modest differences in glycaemic control that was not intensified, incident or worsening nephropathy (progression to macroalbuminuria) was reduced by 39%, with a 44% risk reduction in doubling of serum creatinine. Although there were only small numbers, a 55% relative risk reduction in the need for renal replacement therapy was also seen.²⁷ A more recent evaluation of albuminuria progression confirmed these findings.²⁸

In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) study, the majority of participants (72.4%) had cardiovascular disease at entry and 24.7% had CKD. The mean HbA1c of 8.7% (72 mmol/mol) at entry was set against a target HbA1c of 7% (53 mmol/mol), and the achieved HbA1c with liraglutide of 7.6% (60 mmol/mol) was only 0.4% (4 mmol/mol) lower than in the control group. There was a 22% reduction in the incidence of nephropathy, but solely on the basis of proteinuria reduction, with no impact on more advanced renal measures.²⁹

In the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN -6) with the weekly GLP-1 analogue semaglutide, the most effective glycaemic treatment was achieved using local best practice. Established cardiovascular disease was highly prevalent (83%) and 23.4% of participants had evident CKD at trial entry. From an HbA1c at baseline of 8.7% (72 mmol/mol), the active treatment led to a reduction in HbA1c to 7.3–7.6% (56–60 mmol/mol) depending on the dosage, which was 0.7–1% (7–10 mmol/mol) lower than the control group. New or worsening nephropathy was reduced by 36% with active treatment, essentially through a reduction in progression to macroalbuminuria.³⁰

In these studies, the control group had modestly poorer glycaemic control without these beneficial renal outcomes, which suggests that renoprotective non-glycaemic-based mechanisms may explain the observations.

The following chapters in this guideline will focus in more detail on these studies and the available glucose-lowering therapies for patients who have diabetes and DN-CKD.

At present, it would be prudent to consider an HbA1c target of 58 mmol/mol for most patients with type 2 diabetes and DN-CKD if they are on an insulin-dominant regime, and a target of up to 68 mmol/mol in older patients with more advanced CKD, especially where they have renal anaemia.

It remains to be seen whether it is appropriate and safe to have a lower glycaemic HbA1c target of 52 mmol/mol in patients who are treated with less insulin and more GLP-1- and

SGLT-2 inhibitor-focused treatments when the eGFR is >30 mL/min/1.73 m², both when a patient does and does not have cardiovascular disease.

From the current evidence, there is no basis to seek HbA1c values of lower than 52 mmol/mol in older patients with type 2 diabetes and DN-CKD.

Conclusion

Individualised HbA1c targets should be applied in the management of patients with diabetes and DN-CKD, using the levels suggested in [Table 1](#). It is, however, important to ensure that anaemia has been excluded or considered when using HbA1c to assess glycaemia. In addition, given the potential for the deterioration of renal function over time, at least annual monitoring of GFR is necessary, as this could impact on the type and dosage of diabetes therapies, as well as the appropriate glycaemic target. The selection of individual classes of agent, tailored to the additional comorbidities that are frequently seen alongside DN-CKD, will also influence therapy selection ([Table 2](#)). In addition, certain combinations of different classes of agents would need judicious consideration ([Table 3](#)). Although these current guidelines focus on the individual classes of glucose-lowering agent, combinations of different classes will frequently be used to manage diabetes in patients with CKD. There is a relative dearth of studies that specifically evaluate different drug combinations in patients with kidney disease, and this is clearly an area for both further research and current clinical audit ([Table 4](#)).

Table 1 Glycaemic targets in patients with diabetes and DN-CKD

	Glycaemic target	Note
Type 1 diabetes	48–58 mmol/mol (6.5–7.5%)	Younger patients within 10 years' duration of diabetes and variable microalbuminuria–CKD stage 2
	58–62 mmol/mol (7.5–7.8%)	The majority of patients with proteinuria and/or CKD stages 3–4
	58–68 mmol/mol (7.5–8.5%)	Patients with CKD stage 5-dialysis
Type 2 diabetes	48–58 mmol/mol (6.5–7.5%)	For the majority of patients who are aged <40 years, or have CKD stages 1–2 (no basis to aim for <52 mmol/mol (6.9%) unless the patient is aged <40 years and has CKD stages 1–2)
	52–58 mmol/mol (6.9–7.5%)	For those with CKD stages 3–4 this target may be appropriate with a GLP-1–SGLT-2 inhibitor-based treatment regime without insulin
	58–68 mmol/mol (7.5–8.5 %)	For those with CKD stages 3–4-proteinuria who are on an insulin-based regime, and those with CKD stage 5 who are on dialysis

Table 2 Non-renal and glycaemic contraindications to the selection of blood glucose lowering therapies in patients with DN-CKD

Condition	Drug	Note
Retinopathy	Pioglitazone	Absolute contraindication in diabetic maculopathy
	Semaglutide	Relative contraindication in moderately hyperglycaemic patients (HbA1c >8.5% (68 mmol/mol)) who have moderate to severe diabetic retinopathy: caution is advised
Bone health	Pioglitazone	Absolute contraindication in patients who have had previous osteoporotic fractures; or relative contraindication in those with post-menopausal osteoporosis with neuropathy
	SGLT-2 inhibitors	Relative contraindication of canagliflozin in patients with established osteoporotic fractures; no other current SGLT-2 inhibitor bone health limitations are identified
Feet health	SGLT-2 inhibitors	Absolute contraindication of canagliflozin if a patient has had previous forefoot amputation and/or active diabetic foot disease; relative contraindication of other SGLT-2 inhibitors in similar circumstances: no risk with empagliflozin is identified
Cardiac failure	Pioglitazone	Absolute contraindication in patients with established treated heart failure and where at-risk patients have a raised serum brain natriuretic peptide (BNP)
	Saxagliptin	Absolute contraindication in patients with treated established heart failure
Pancreatic health	GLP-1 analogues	Absolute contraindication of GLP-1 analogues where a patient has previously documented pancreatitis; relative contraindication in patients who are at risk of pancreatitis with raised triglycerides, those on steroid therapy, those using other agents that are associated with pancreatitis or those with documented alcoholism
Bladder health	SGLT-2 inhibitors Pioglitazone	Relative contraindication of all medications in this class in patients who have documented neuropathic bladder and recurrent urinary infections Bladder cancer – no current absolute contraindication to continuation of pioglitazone and SGLT-2 inhibitors; relative contraindication/caution to initiation of pioglitazone and SGLT-2 inhibitors in those with bladder cancer or without investigation of unexplained haematuria
Biliary tract health	Liraglutide	Relative contraindication if a patient has active gall bladder disease

Table 3 Cautions when using combinations of drug classes to treat diabetes in patients who have CKD

1	Insulin and sulfonylurea combination in patients with more advanced CKD (stages 4–5)
2	SGLT-2 inhibitors and pioglitazone combination in patients with evident metabolic bone disease
3	Insulin and pioglitazone combination in patients with documented fluid retention and/or a high risk of (or established) cardiac failure
4	The lack of clinical benefit with the combination of DPP-4 inhibitor and GLP-1 analogue

Traditionally, the licensing of medicinal products in relation to renal dysfunction utilised CrCl to define cut-off points. With the advent of equation related estimated GFR (eGFR), we would no longer recommend measuring CrCl, which is less reliable in the clinic environment. We would recommend that eGFR is utilised, preferably using the more accurate Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation when determining whether certain therapies they can be used or for adjusting medication dosages in diabetes.³¹

It is important to recognise that eGFR equations that are currently in use underestimate kidney function in obese patients (BMI >30 kg/m²) with type 2 diabetes.³² In these circumstances, the Cockcroft–Gault equation could be used (www.kidney.org/professionals/KDOQI/gfr_calculatorCoc) as long as there is appropriate sick day guidance in effect and that the kidney function is monitored appropriately to ensure that the treatment is stopped when the renal function moves out of the licensing range.

Table 4 Practical advice for healthcare workers who are managing patients with type 2 diabetes and CKD (eGFR level) and action to be taken

eGFR level	Medication and action to be taken		
	Pioglitazone	Nateglinide and repaglinide	Metformin
For all patients	<ul style="list-style-type: none"> Exclude a past medical history of bladder cancer or uninvestigated haematuria, heart failure or significant fluid retention. Practitioners should weigh up the glycaemic benefit of pioglitazone against the risk of bone fractures. Consider discontinuing pioglitazone in patients who develop osteoporotic fractures. 	<ul style="list-style-type: none"> Practitioners have to weigh up the risk of hypoglycaemia. 	<ul style="list-style-type: none"> Practitioners have to weigh up the glycaemic and cardiovascular benefits against the rare risk of associated lactic acidosis. Practitioners should provide all patients with the information leaflet <i>Advice for patients taking metformin</i>.
>60 mL/min/1.73 m ²	<ul style="list-style-type: none"> No renal contraindication to pioglitazone. 	<ul style="list-style-type: none"> Continue or commence nateglinide or repaglinide. Advise patients to monitor their capillary blood glucose (CBG) 2 hours after taking the medication and to take precautions when driving. 	<ul style="list-style-type: none"> No renal contraindication to metformin. Some of these patients are at increased risk due to other risk factors (see advice for increased vigilance groups in the bottom row of this table).
45–60 mL/min/1.73 m ²	<ul style="list-style-type: none"> Continue use of pioglitazone in patients who are established on the agent but monitor for fluid retention 3–6/12ly thereafter. For new patients who have no major fluid retention, pioglitazone can be started at 15 mg once daily, and titrated up, based on the effectiveness and development of fluid retention in 2/52ly. 		<ul style="list-style-type: none"> Continue use in patients who were established on the agent, but review the dose in light of glucose control needs. For new patients who have no major active comorbidities, metformin commencement can be considered if age-related life expectancy is normal and vascular/diabetes risks are present. Increase monitoring of renal function (to every 3–6 months).
30–45 mL/min/1.73 m ²	<ul style="list-style-type: none"> In patients who are established on pioglitazone, monitor for fluid retention every 3–6/12ly. Patients can be started at 15 mg once daily and titrated up, based on the effectiveness and development of fluid retention in 2/52ly. 		<ul style="list-style-type: none"> Continue or commence metformin with caution and explain the risks and benefits to the patient. Use the lowest dose that achieves glycaemic control (suggest a 50% dose up to 1,000 mg/day). Closely monitor renal function (every 3 months).

<30 mL/min/1.73 m ²	<ul style="list-style-type: none"> • In patients who are established on pioglitazone, monitor for fluid retention 3/12ly. • Patients can be started at 15 mg once daily and titrated up, based on the effectiveness and development of fluid retention in 2/52ly. 	<ul style="list-style-type: none"> • Review the dose of nateglinide or repaglinide if the patient is already taking it, and consider a reduction based on their CBG. • Advise patients to monitor their CBG 2 hours after taking medication and to take precautions when driving. • Commence nateglinide or repaglinide at half the regular dose. 	<ul style="list-style-type: none"> • At this level of renal function we cannot give firm recommendations about the ongoing use of metformin. • Some specialists may choose to use the agent in selected patients where they see that the benefits outweigh the risks. • Pharmacokinetic work would suggest that if metformin is used, a dose of 500–1,000 mg/day would result in 95% of people having peak metformin concentrations of <5 mg/L. • Consider measuring the true GFR directly, especially in patients who are obese. The Cockcroft–Gault formula may give a better reflection of eGFR in obese patients, and may allow the safe use of metformin in patients who have a low GFR.
Dialysis	<ul style="list-style-type: none"> • Patients can be started at 15 mg once daily and titrated up, based on the effectiveness and development of fluid retention in 2/52ly (note the risk of fluid retention is offset by dialysis). • In patients who are established on pioglitazone, monitor for fluid retention 3/12ly. 	<ul style="list-style-type: none"> • Not licensed, but not contraindicated, so it can be considered. • Continue or commence repaglinide at half the regular dose. • Advise patients to take precautions when driving. • Increased monitoring is required while a patient is on these agents. 	
AKI (or at risk of AKI)		<p>Review and consider (temporarily) stopping* metformin in patients who:</p> <ul style="list-style-type: none"> • have acute changes in renal function (a fall in eGFR of >10 mL/min/1.73 m² over a period of days or weeks) • <i>are at risk</i> of AKI such as: <ul style="list-style-type: none"> ○ acute volume depletion and dehydration eg gastrointestinal upset, stomas, change in diuretic dose ○ during operative procedures with a high risk of <i>hypotension or volume depletion</i> ○ in the presence of <i>hypotension</i> or shock, eg severe infection ○ intravascular administration of iodinated contrast agents (stop metformin on the day of and 2 days after X-ray related intravenous contrast use) 	

		<ul style="list-style-type: none"> ○ co-administration with nephrotoxic drugs, eg non-steroidal anti-inflammatory drugs (NSAIDs) ○ patients with acute illness who are also on drugs that are known precipitants of AKI in association with any angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) (such as non-steroidal anti-inflammatory drugs (NSAIDs)), especially combined with diuretics <ul style="list-style-type: none"> ● those with previous episodes of AKI. <p>*Duration of stopping metformin should be based on the likely period of risk. In general it should be resumed at a low dose after discharge.</p>
Recovery from AKI		<ul style="list-style-type: none"> ● Once urine flow has returned to normal and GFR is >30 mL/min/1.73 m², resume metformin at a low dose (eg 500–1,000 mg/day). ● Monitor glucose control in outpatients and primary care before considering the further need for increasing doses.
Increased vigilance		<p><i>Increased vigilance</i> is needed for the following groups of patients who are likely to be at a higher risks of lactic acidosis even with normal renal function:</p> <ul style="list-style-type: none"> ● those with decompensated cardiac or respiratory failure ● those with acute conditions that may cause tissue hypoxia, eg recent myocardial infarction (MI) or shock ● those with hepatic insufficiency, acute alcohol intoxication or alcoholism.

2 Insulin therapy

Recommendations

- 1 There is no firm evidence that insulin therapy reduces the risk of progressive renal disease. Therefore the aim of insulin therapy should be to improve glycaemic control and improve quality of life, with a low risk of hypoglycaemia (Grade 1C).
- 2 Insulin requirements are likely to rise in the early stages of diabetic nephropathy (DN) due to increased insulin resistance (Grade 1C).
- 3 As glomerular filtration rate (GFR) declines, insulin requirements are likely to diminish through reduced renal insulin clearance, and doses should be reduced as GFR declines, especially in chronic kidney disease (CKD) stage 3b and below. In patients with CKD stage 3b and below who are on insulin, and whose HbA1c is 58 mmol/mol or below, a reduction of insulin doses should be considered (Grade 1C).
- 4 Patients with diabetes and CKD who are treated with insulin should undertake regular glucose monitoring and be encouraged to manage their own diabetes as far as possible (Grade 1C).
- 5 In patients who are less likely to be able to comply with the requirements of a basal bolus regime, once daily regimes with longer-acting insulins should be considered (Grade 1D).
- 6 If patients have troublesome hypoglycaemia on neutral protamine Hagedorn (NPH) insulin, conversion to analogue insulins may be of benefit (Grade 1C).
- 7 There is no evidence of benefit from biphasic premixed insulin administered once, twice or three times daily in patients with CKD stages 3–5. This regimen, however, may be useful in individual patients who have poorly controlled diabetes on a once daily insulin regimen (Grade 2C).
- 8 Care should be taken when combining insulin with a sulfonylurea in patients with CKD stages 3–5, due to the high risk of hypoglycaemia (Grade 1B).

Areas that require further research

- 1 Does insulin therapy reduce the risk of progressive renal disease in patients with DN?
- 2 Is there a role for 50:50 mixed insulins in patients with DN and progressive renal disease?
- 3 Is there a role for continuous subcutaneous insulin infusion (CSII) in patients with DN and progressive renal disease?
- 4 Is there a role for biosimilars or insulin–GLP-1 analogue mixtures in patients with CKD?
- 5 What is the efficacy and safety of different insulin regimes in combination with a sulfonylurea at different stages of CKD?

Audit standards

- 1 The proportion of patients with CKD stage 3b and below who are on insulin and whose HbA1c is 58 mmol/mol or below, whose insulin dose has been reduced.
- 2 The proportion of insulin-treated patients with CKD stage 3b and below who are assessed for frequency and awareness of hypoglycaemia and have recorded severe acute hypoglycaemia episodes that required ambulance assistance.
- 3 The proportion of patients who have an eGFR of <60 mL/min/1.73 m² (or <45 mL/min/1.73 m² on insulin therapy) in combination with sulfonylureas, and HbA1c values below 53 mmol/mol.

The role of the kidneys in glucose/insulin homeostasis

While the liver, pancreas and skeletal muscles play central roles in glucose homeostasis, the role of the kidneys is somewhat underappreciated. In the fasting (post-absorptive) state, the kidneys are responsible for around 25% of glucose that is released into the plasma via gluconeogenesis, and glucose utilisation by the kidneys in the fasting state accounts for around 10% of total body glucose utilisation.³³ Around 180 g of glucose is filtered by the kidneys in 24 hours, most of which is reabsorbed via the proximal tubular sodium glucose co-transporter-2 (SGLT-2).³⁴ In type 2 diabetes, renal gluconeogenesis, glucose uptake and renal glucose reabsorption are all increased.³⁵ Furthermore, in people with diabetes, the relative increase in renal gluconeogenesis is significantly greater than the increase seen in hepatic gluconeogenesis (300% versus 30%).³³

In normal subjects, the kidneys play an important role in insulin metabolism. Insulin is freely filtered at the glomerulus, and 60% of renal insulin clearance relies on glomerular filtration, while the remaining clearance is via the peritubular vessels.³⁶ Renal insulin clearance is around 200 mL per minute: higher than normal GFR due to the contribution of renal tubular secretion.³⁷ Therefore, around 6–8 units of insulin are metabolised by the kidneys each day, equating to around a quarter of pancreatic insulin secretion in non-diabetic individuals. In people with diabetes who are treated with exogenous insulin therapy, the contribution of the kidneys to insulin metabolism may be greater, due to the lack of first-pass metabolism by the liver when insulin is given subcutaneously. It is estimated that 30–80% of systemic insulin may be metabolised by the kidneys, which highlights an important role of the kidneys in the metabolism of exogenous insulin.³⁸

Glucose homeostasis in CKD

CKD is an insulin-resistant state. A number of mechanisms have been suggested to explain this state, including the presence of 'uraemic toxins',³⁹ excess parathyroid hormone due to deficiency of active 1,25-dihydroxyvitamin D,⁴⁰ or anaemia⁴¹ leading to reduced skeletal muscle glucose uptake and diminished glycogen synthesis. These hypotheses are evidenced by the fact that dialysis can significantly improve insulin sensitivity by removing uraemic toxins;⁴² the fact that the administration of active vitamin D (1,25-dihydroxyvitamin D) may enhance insulin sensitivity;⁴³ and the fact that improved glucose uptake is seen following the correction of anaemia with erythropoietin.⁴⁴

A reduction in GFR may lead to a reduction in insulin clearance rate, and this is most marked at very significant levels of renal impairment (GFR <20 mL/min/1.73 m²), because increased tubular uptake is able to compensate to some extent. Once GFR is sufficiently low, however, insulin clearance may become markedly reduced, leading to higher levels of circulating insulin and a significantly increased risk of hypoglycaemia.^{45,46}

Insulin secretion can also be impaired in uraemia. Metabolic acidosis seen in renal impairment may lead to the suppression of insulin release,⁴⁷ and elevated parathyroid hormone may also lead to increased intracellular calcium, which blunts the release of insulin from pancreatic β -cells. Deficiency of 1,25-dihydroxyvitamin D may also be important in insulin secretion, and the administration of active vitamin D enhances insulin release.⁴³

Insulin therapy in patients with CKD stages 1–3

Many oral hypoglycaemic therapies are contraindicated in CKD or may be ineffective in patients with long-standing type 2 diabetes, and hence insulin therapy is frequently required. A common clinical scenario is the cessation of metformin or other glucose-lowering therapies as GFR declines, which necessitates insulin therapy to maintain glycaemic control.

It is frequently noted that insulin requirements follow a biphasic course in progressive renal disease. In the early stages of diabetic nephropathy (DN)-CKD, resistance to the effects of insulin predominates and may worsen, leading to a greater requirement for insulin.⁴⁸ Indeed, the presence of micro- or macroalbuminuria is noted to be strongly associated with insulin resistance.⁴⁹ Insulin requirements, therefore, are frequently higher in early DN-CKD, when albuminuria predominates. As GFR declines, however, insulin requirements may diminish, with some studies suggesting a 30% reduction in insulin requirements when the GFR is <60 mL/min/1.73 m², compared with when the GFR is >90 mL/min/1.73 m².^{50–52}

The use of insulin therapy in patients with DN-CKD and mild or moderate CKD has not been subject to randomised study. The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) randomised trial, however, compared glycaemic control with insulin-sensitisation therapy to that with insulin-provision therapy in 1,799 patients with type 2 diabetes and coronary artery disease (CAD), and monitored albumin:creatinine ratio (ACR) over 5 years.⁵³ Despite mean glycated haemoglobin (HbA1c) levels being lower in the insulin-sensitisation group compared with the insulin-provision group, the ACR increased over time in the insulin-sensitisation group and was stable in the insulin-provision group, which suggests a protective effect of insulin. Similarly, the effect on ACR of the use of continuous subcutaneous insulin infusion (CSII) compared with multiple daily insulin (MDI) therapy has been examined.⁵⁴ After 4 years, patients in the CSII group had better glucose control and lower ACR change, compared with the MDI group (–10.1 (–13.3; –6.8) versus –1.2 (–3.6; 0.9); $p < 0.001$). Also, reduction in ACR was significantly associated with CSII treatment, after adjustment for other factors. The authors suggested that this effect may be due to reduced glycaemic variability, but there is a need for confirmation in randomised controlled trials.

Use of analogue insulins as opposed to human insulins has been suggested as being protective in patients with DN-CKD, but relevant studies have been small and short term. One study of insulin pharmacokinetics in a small number of patients with type 1 diabetes with and without nephropathy showed that glucose profiles were more responsive to analogue insulin compared with human insulin.⁵⁵ In patients with type 2 diabetes and albuminuria, one study suggested that insulin lispro may prevent glomerular hyperfiltration and reduce the renal effects of meal-associated hyperglycaemia.⁵⁶

Use of biosimilar insulins (insulin glargine biosimilar, Abasaglar®) and combined insulin / GLP-1 analogue therapies (IDegLira® and LixiLan®) have not been evaluated in patients with renal disease.

Insulin therapy in patients with CKD stages 4–5 (pre-dialysis)

In patients with CKD stage 4 and below, insulin resistance and impaired insulin secretion remain problematic, due to the factors outlined above (acidosis, anaemia and abnormal vitamin D metabolism). In addition, however, the loss of clearance of insulin and reduction in gluconeogenesis in the kidneys often lead to falling insulin requirement and, subsequently, to a higher risk of hypoglycaemia if insulin is not reduced.⁴¹ In addition, uraemia-induced

anorexia and weight loss may also occur, leading to significant reductions in insulin requirement. Occasionally, insulin requirements may fall low enough to obviate the need for insulin and allow conversion to oral therapy or the cessation of therapy altogether.⁵⁷ Some guidelines suggest a gradual reduction of the total daily insulin dose to 75% when the GFR is 10–50 mL/min/1.73 m², and to 50% for a GFR of <10 mL/min/1.73 m².^{58,59}

The use of insulin therapy or the type of insulin therapy has not been subjected to randomised study in patients with CKD stages 4–5. One study suggests that a lower weight-based calculation of insulin dosage (0.5 versus 0.25 units/kg/day) in patients with a GFR of <45 mL/min/1.73 m² resulted in lower rates of hypoglycaemia, without compromising control of glycaemia.⁶⁰ A further study suggests that the use of insulin glargine in patients with type 2 diabetes and renal impairment may lead to improved control.⁶¹ This study examined 89 patients with diabetes and a GFR of around 30 mL/min/1.73 m² who were treated with oral antidiabetic drugs or NPH insulin and had sub-optimal glycaemic control or frequent hypoglycaemic episodes. Such patients were converted to insulin glargine, with additional fast-acting insulin if required. Glucose control improved significantly without increased hypoglycaemic events. A recently published pharmacokinetic study using insulin degludec in patients with renal impairment suggested that the pharmacokinetic properties of insulin degludec were preserved in subjects with renal impairment, including in subjects with end-stage renal disease,⁶² suggesting that no dose adjustment is needed with degludec in patients with significant renal impairment.

Insulin therapy in patients with end-stage renal failure

Insulin therapy in patients with diabetes who are on haemodialysis is dealt with in guidelines that have been produced by the Joint British Diabetes Societies and the Renal Association.⁶³

The use of insulin in combination with a sulfonylurea for patients who have CKD at all stages should take account of the increased risk of hypoglycaemia (especially in those with CKD stage 3b or above), although the current evidence base for the enhanced risk is not strong.⁶⁴

3 Sulfonylureas

Recommendations

- 1 Patients with type 2 diabetes and chronic kidney disease (CKD) who are on sulfonylurea (SU) treatment are at increased risk of hypoglycaemia. We therefore advise regular capillary blood glucose (CBG) monitoring in this patient group. For patients who have an estimated glomerular filtration rate (eGFR) of <45 mL/min/1.73 m², CBG monitoring should be mandatory (Grade 2B).
- 2 Gliclazide and glipizide are metabolised in the liver and are therefore the preferred SUs for patients with type 2 diabetes and CKD. Given the absence of excess cardiovascular events in a randomised trial, gliclazide should be the preferred choice of drug (Grade 1B).
- 3 We suggest that a sub-maximal dosage of gliclazide and glipizide is used in patients with an eGFR of <45 mL/min/1.73 m² (Grade 2B).
- 4 We suggest that SUs should be avoided alongside insulin in patients with an eGFR of <45 mL/min/1.73 m², unless there is clear evidence of the absence of hypoglycaemia (Grade 2B/C).
- 5 We suggest that gliclazide and glipizide should be avoided when a patient's eGFR is <30 mL/min/1.73 m², as this therapy is off licence in this scenario (Grade 2B).
- 6 The safety profiles and pharmacokinetics of glibenclamide, glimepiride and tolbutamide do not support their use in patients with CKD, and we suggest that they should be avoided in such patients (Grade 2B).

Areas that require further research

- 1 What is the relationship between SUs and hypoglycaemia (with or without concomitant insulin therapy) in patients with CKD?
- 2 What is the SU-related mortality in patients with CKD?
- 3 A head-to-head comparison of the efficacy and hypoglycaemic risk between gliclazide/glimepiride and insulin or in combination.

Audit standards

- 1 The proportion of patients with CKD who are on SUs and who regularly monitor their CBG.
- 2 The proportion of patients with an eGFR of <30 mL/min/1.73 m² who are on SUs and who regularly monitor their CBG.
- 3 The proportion of patients who are on individual SUs, according to CKD stage and frequency of severe acute hypoglycaemic episodes (SAHE), who have recorded ambulance call outs and hospital admissions.
- 4 The proportion of patients with an eGFR of <60 (and <45) mL/min/1.73 m² who are on SUs, and the dosage used.
- 5 The proportion of patients with an eGFR of <60 (and <45) mL/min/1.73 m² who are on SUs in combination with insulin therapy who have an HbA1C of 53 mmol/mol ($<6.5\%$).

- 6 The documented sick day guidance that is provided to patients with CKD who are on SUs and other agents.

Evidence base

SUs work by closing adenosine triphosphate (ATP)-sensitive potassium channels at β -cells and therefore triggering insulin release. They also improve insulin sensitivity by stimulating transmembranous glucose receptors in muscle and fat cells.

The first generation SUs (tolbutamide and chlorpropamide) were followed by the second generation SUs (including glibenclamide, gliclazide and glipizide) and third generation SUs (namely glimepiride).

SUs are metabolised by hepatic cytochrome P450 CYP2C9, although the clearance of metabolites (and unchanged drugs for certain SUs) is partly through the kidneys for most SUs. Therefore, accumulation in renal failure patients, including those on dialysis, may predispose patients to a risk of hypoglycaemia.

SUs should be used with caution in patients who have a glucose-6-phosphate dehydrogenase (G6PD) deficiency, and should not be used in those with insulin-dependent diabetes, diabetic coma, ketoacidosis, or those who are lactating or pregnant. Key side effects to be considered for the use of SUs are increased body weight (1.7 kg more than the placebo within 10 years)⁶⁵ and risk of hypoglycaemia,⁶⁶ which is even higher in patients with CKD.

There is very little comparative randomised controlled trial evidence of the use of SUs in those with CKD. There is an absence of clear licensing that supports their use in the presence of severe renal impairment (defined by creatinine clearance (CrCl) of <30 mL/min) and dose adjustments may become necessary in patients with moderate renal impairment (initially defined by CrCl of 30–50 mL/min). The initial licences for SUs predate the current CKD classification based on eGFR, and this discrepancy undermines the applicability of these studies to current practice. It should be noted that SUs are generally highly protein-bound and are therefore unlikely to be dialysed. This can cause post-dialysis hypoglycaemic episodes to occur. Use of SUs in patients with type 2 diabetes on haemodialysis is off licence.

The risk of hypoglycaemia in concomitant diabetes and CKD and the effect of SUs

Hypoglycaemia is more common in patients with CKD, due to reduced oral intake and decreased insulin clearance via the kidneys. In a retrospective cohort analysis of patients with diabetes from the Veterans Health Association, the incidence rate of hypoglycaemia doubled with an eGFR drop to <60 mL/min/1.73 m² (10.72 versus 5.33 per 100 patient months).⁶⁷

Bodmer *et al*⁶⁶ analysed the UK General Practice Research Database and demonstrated that CKD carries a 58% increased risk of hypoglycaemia (odds ratio (OR) 1.58 (1.25–2)). When they compared the drug effect, the risk with SUs was much greater than with metformin (2.79 (95% confidence interval (CI) 2.23–3.50)). The study did not specifically look into risk with the concomitant use of SUs and the presence of CKD.

More recently, a cardiovascular outcome randomised multicentre trial in 3,028 patients with type 2 diabetes who were on metformin compared the effect of SUs (gliclazide 30–120 mg/day or glibenclamide) and pioglitazone, and confirmed that severe and moderate

hypoglycaemic episodes were more frequent in patients who were treated with SUs than with pioglitazone (severe 0% v 2%, $p < 0.01$; moderate 32% v 10%, $p < 0.01$).⁶⁸

Hypoglycaemia is underreported due to testing limitations, legal implications for driving and impaired warning signs. Due to the increased cardiovascular disease burden in patients with diabetes and CKD, it is considered that hypoglycaemic episodes could trigger fatal cardiovascular events, but it is difficult to prove this in an appropriately designed clinical trial. In the Thiazolidinediones or Sulphonylureas and Cardiovascular Accidents Intervention Trial (TOSCA.IT), there were no cardiovascular outcome differences in patients who were treated with either SUs or pioglitazone in addition to metformin, but this trial was designed with higher cardiovascular risk presumption and the event rate was relatively low (half that seen in the PROactive trial). At the start of the study, 21% of patients in both groups had microalbuminuria and the nephropathy progression rate over 5 years was the same (at 23%).⁶⁸

In theory, the combination of an SU and insulin in CKD might be considered to pose a greater risk of hypoglycaemia. One retrospective cohort study examined the risk of cardiovascular disease and hypoglycaemia among US veterans who were treated with an SU who either switched to or added insulin therapy, with hazard ratios (HRs) calculated for those with an eGFR of 15–60 mL/min/1.73 m². Among the group who had CKD, there was no suggestion that either composite cardiovascular disease or new CKD or first hypoglycaemic events were more common among those who were treated with SUs who additionally received insulin.⁶⁹

Gliclazide

Gliclazide is metabolised in the liver to inactive metabolites that are eliminated in the urine. Due to the increased risk of hypoglycaemia with advancing CKD, the dose of gliclazide might need to be reduced. Dose reduction is best guided by CBG monitoring. The summary of product characteristics (SPC) states that it is contraindicated in 'severe renal failure' (no eGFR given),⁷⁰ but it is not uncommon for it to be prescribed off licence in severe CKD. Ninety-five percent of gliclazide in serum is protein-bound, hence it is unlikely to be dialysed. In a study of insulin secretagogues-related mortality based on the Danish National Diabetes Register, gliclazide was the only SU that was not associated with an increased risk of death (1.05 (0.94–1.16)).⁷¹ In the TOSCA.IT study, 21% of participants had microalbuminuria at baseline, and those with a serum creatinine of >132 µmol/L were excluded from the trial. Gliclazide was used at a submaximal dosage of 30–120 mg daily. Analyses pre-specified an eGFR of < and > 60 mL/min/1.73 m². There were no differences in new or worsening nephropathy, or in albuminuria progression between the SU and the pioglitazone comparator group, and these findings were observed regardless of participants' eGFR category.⁶⁸

Glimepiride

Glimepiride is metabolised in the liver to two major metabolites with preserved hypoglycaemic activity. In renal disease, these metabolites accumulate. Although the half-life of glimepiride is 5–7 hours, the drug can cause severe hypoglycaemia that lasts more than 24 hours. In CKD stages 4 and below, the use of glimepiride is dangerous and contraindicated.⁷²

Glipizide

The metabolism of glipizide mainly occurs in the liver. The primary metabolites are inactive hydroxylation products and polar conjugates, and they are excreted mainly in the urine. Less than 10% of unchanged glipizide is found in urine. In terms of licensing, glipizide is contraindicated in severe renal failure. Glipizide is unlikely to be dialysed by either peritoneal dialysis or haemodialysis.⁷³

The efficacy and safety of sitagliptin (25–50 mg based on the patient's eGFR) and glipizide (2.5–10 mg based on the patient's response) monotherapy in patients with type 2 diabetes and moderate/severe CKD (off licence) were assessed in a 54-week, randomised, double-blind, parallel-arm study. Both drugs caused a comparable HbA1C reduction (0.6% and 0.8% for glipizide and sitagliptin, respectively). Glipizide, however, caused more symptoms of severe hypoglycaemia (17.0% v 6.2%, $p=0.001$, but no measurement of glucose required for confirmation) and increased weight (difference: 1.8 kg; $p=0.001$).⁷³ Symptoms of hypoglycaemia cannot be relied upon in patients with CKD, as hypoglycaemic awareness is often reduced; hence, CBG monitoring is necessary.

Tolbutamide

Tolbutamide is contraindicated in those with severe renal impairment. It is unlikely to be dialysed by either peritoneal dialysis or haemodialysis.⁷⁴

Glibenclamide

Glibenclamide (glyburide) is metabolised in the liver and excreted equally by the kidneys and intestine. Some metabolites are active and can accumulate in CKD despite the fact that biliary removal partially counteracts the limited renal excretion. Hypoglycaemia may be serious and can last for >24 hours in patients with CKD.^{75,76}

The use of glibenclamide in patients with decreased renal function should be limited and it is contraindicated in those with severe renal failure.⁷⁷

4 Meglitinides

Recommendations

- 1 Meglitinides can be considered for use in patients with type 2 diabetes and chronic kidney disease (CKD) as a monotherapy (repaglinide) or in addition to metformin (nateglinide and repaglinide) if other agents are not tolerated (Grade 2C).
- 2 In patients with type 2 diabetes who are on meglitinides, consider the risk of hypoglycaemia and advise them about capillary blood glucose (CBG) monitoring accordingly (Grade 1D).
- 3 Meglitinide dose reduction is advised in patients with CKD stages 4 and 5 who are on dialysis (Grade 2C). In these patients, due to hepatic metabolism, repaglinide is advised in preference to nateglinide (Grade 2C).

Areas that require future research

- 1 The clinical outcomes of meglitinides treatment in patients with type 2 diabetes and CKD.
- 2 The efficacy and safety of meglitinides in patients with type 2 diabetes and all stages of CKD in attaining and retaining glucose control as mono, dual and triple therapy.
- 3 The efficacy and safety of meglitinides with background insulin in patients with type 2 diabetes and CKD.

Audit standards

- 1 The percentage of patients with type 2 diabetes and CKD who use meglitinides as mono or dual therapy, across the range of eGFRs.
- 2 The percentage of patients with type 2 diabetes and CKD who are on meglitinides and are advised to monitor their CBG, across the range of eGFRs.
- 3 The percentage of patients with an eGFR of <30 mL/min/1.73 m² in whom the dose of meglitinides is reduced.

Evidence base

Nateglinide and repaglinide are rapid-onset, short-acting insulin secretagogues that lower postprandial hyperglycaemia in patients with type 2 diabetes. Due to their characteristics, unlike other oral hypoglycaemic drugs, they provide the benefit of flexibility in eating and dosing, but require multiple daily administration. They are licensed for use as monotherapy (repaglinide) or in addition to metformin (nateglinide and repaglinide).^{78,79} The main side effect of nateglinide and repaglinide is hypoglycaemia. Both agents are metabolised predominantly in the liver via cytochrome P450 enzymes; therefore, all drugs that induce or inhibit the enzymes alter their plasma concentrations. While repaglinide is eliminated

via bile, metabolised nateglinide, with preserved glucose-lowering properties, is excreted renally. Nateglinide and repaglinide offer additional treatment options in patients with type 2 diabetes and CKD.

Nateglinide

No clinical outcomes have been reported from clinical trials with nateglinide.

A 1-year, double-blind, placebo-controlled study of the efficacy of nateglinide (n=133) against gliclazide (n=129) in addition to metformin found no difference between them (HbA1c reduction was 0.41% for nateglinide plus metformin and 0.57% for gliclazide plus metformin). In that study, nateglinide had a better safety profile than gliclazide in patients with CKD, due to the lower risk of hypoglycaemia.⁸⁰

Nateglinide is metabolised in the liver, but its main metabolite retains a glucose-lowering effect.⁷⁸ Renal impairment does not significantly alter the excretion of nateglinide, and it is licensed for use in patients with all stages of CKD. When renal function is impaired, however, nateglinide's main metabolite is accumulated and significantly cleared by dialysis.^{81,82} It is recommended that the dose of nateglinide is reduced in patients with advanced renal failure.

A retrospective subgroup analysis from all completed nateglinide studies in high-risk patients (ie those with the following characteristics: estimated creatinine clearance (CrCl) of <60 mL/min, aged over 64 years and +/- low baseline HbA1c of <7.5%) looked into the efficacy and safety of nateglinide monotherapy. Nateglinide was found to be effective and well-tolerated in these patients. The risk of documented moderate and severe hypoglycaemia increased by 0.8% in patients with CrCl of <60 mL/min, compared with patients with normal renal function.⁸³ A 2-week study of nateglinide in renal transplant patients demonstrated a significant improvement in postprandial hyperglycaemia; better insulin response following a standardised meal; and a good side-effect profile.⁸⁴

Repaglinide

Repaglinide's efficiency at lowering HbA1C (0.58%) is similar to glibenclamide, and slightly better than glipizide. There is a lower incidence of severe hypoglycaemia, which makes it a more attractive treatment option for patients with type 2 diabetes who also have CKD. The incidence of hypoglycaemia is comparable to that of gliclazide.⁸⁵ Repaglinide is metabolised in the liver and <8% of it is excreted unchanged via the kidneys. In patients with advanced renal failure, the concentration of repaglinide does increase, but at a level that is not considered to be metabolically relevant.⁷⁹ Haemodialysis does not change clearance of repaglinide.⁸⁶

The Multinational Repaglinide Renal Study Group conducted an open-label safety and efficiency study in patients with type 2 diabetes and a CrCl of <60 mL/min and >20 mL/min (n=130), and those with type 2 diabetes and normal renal function (n=151) (6-week run-in, 1–4 weeks' repaglinide titration up to 4 mg three times daily and 3-month maintenance). There was no difference in adverse events or hypoglycaemic episodes (defined by symptoms that were confirmed by measurements whenever possible, or biochemically as glucose \leq 2.5 mmol/L) with repaglinide and renal impairment. There were three deaths during the repaglinide treatment period, which were all judged to be unrelated to the

treatment, including one case of sudden death in the renal impairment group. The percentage of patients who had detectable repaglinide in fasting bloods increased with advancing renal failure, but the dose was too low to be considered metabolically relevant.⁸⁷

Cardiovascular safety

The cardiovascular safety profile of meglitinides is largely unknown. Compared with metformin, repaglinide treatment was not associated with increased mortality and cardiovascular risk in a large cohort of patients from the Danish National Registry who were followed for up to 9 years.⁸⁸

Areas of concern

Similar to all insulin secretagogues, the side effects of meglitinides include weight gain and hypoglycaemia. In a meta-analysis of six randomised controlled trials that included 1,326 patients, the rate of weight gain with meglitinides was the same as with gliclazide. The same study found the incidence of hypoglycaemia to be comparable between the two drugs, but the level of evidence was low.⁸⁹ This is in contrast with Ristic *et al*,⁸⁰ who found nateglinide to have a lower rate of hypoglycaemia than glibenclamide, which can be related to its lower efficacy at glucose lowering. The meglitinides class of drugs should be used with caution when liver disease is present, due to the hepatic metabolism.

In summary, nateglinide and repaglinide are attractive treatment options, but they are under-evidenced in patients with type 2 diabetes and all stages of CKD, including those who are on dialysis, because they provide flexibility in terms of dosing. Due to its slightly lower glucose-lowering effect, the risk of hypoglycaemia might also be reduced with nateglinide. It is recommended that the doses of both meglitinides should be reduced in patients with advanced CKD (eGFR of <30 mL/min/1.73 m²), with repaglinide having preferred metabolism to nateglinide. See [Table 4](#) for advice for healthcare workers who are managing type 2 diabetes with nateglinide and repaglinide in patients who have CKD.

5 Metformin

Recommendations

- 1 Metformin can be used in patients who have diabetes, down to an estimated glomerular filtration rate (eGFR) of 30 mL/min/1.73 m². The dosage should be reduced after the eGFR falls below 45 mL/min/1.73 m² (Grade 1B).
- 2 It should be recognised that, in certain circumstances, the eGFR may not give a true reflection of the actual GFR: for example in obese patients. In these circumstances, estimates of GFR using the cystatin C or Cockcroft–Gault formula may give a better estimate of GFR and enable metformin to be used even when the indirect eGFR might contraindicate its use (Grade 1C).
- 3 Metformin should be withheld during periods of acute illness, particularly when a patient has acute kidney injury (AKI). All patients who are treated with metformin should be given sick day guidance ([Appendix B](#)) (Grade 1B).
- 4 Metformin should be withheld prior to and shortly after any procedure that requires the use of radiographic contrast media (Grade 1B).

Areas that require further research

- 1 Does metformin reduce the risk of cardiovascular disease in patients with diabetes and chronic kidney disease (CKD)?
- 2 Can metformin be used safely in patients who have more significant degrees of renal impairment (CKD stages 4–5) by monitoring circulating levels of metformin?
- 3 What effect does the cessation of metformin have on glucose control and renal decline?
- 4 How common is vitamin B₁₂ deficiency in patients with CKD who are on metformin?

Audit standards

- 1 The proportion of patients with CKD on metformin who have received sick day guidance ([Appendix B](#)).
- 2 The proportion of patients in whom metformin is stopped during acute illness, but in whom metformin is restarted on recovery.
- 3 The proportion of patients with CKD who are on metformin and who have anaemia and/or neuropathy who have been tested for vitamin B₁₂ deficiency.

Use of metformin in patients with diabetes

Metformin has been used as a first-line oral agent for patients with type 2 diabetes for over 40 years and it is endorsed by the National Institute for Health and Care Excellence (NICE) and all major professional diabetes groups.⁹⁰ It is an inexpensive, safe and very effective agent that is not associated with either hypoglycaemia or weight gain, both of which occur with diabetes therapies such as sulfonylureas and insulin. The prescription of metformin in patients with type 2 diabetes can be associated with gastrointestinal side effects at any time, which may settle down over time and can be minimised with post-prandial timing and dosage adjustment, or conversion to sustained release preparations. The use of metformin, however, has also been associated with very rare cases of lactic acidosis that continue to receive attention in the medical literature.

The *British National Formulary* states: 'Use with caution in renal impairment – increased risk of lactic acidosis; avoid in significant renal impairment'. NICE recommends:

that the dose should be reviewed if eGFR less than 45 mL/minute/1.73 m² and to avoid if eGFR less than 30 mL/minute/1.73 m². Withdraw or interrupt treatment in those at risk of tissue hypoxia or sudden deterioration in renal function, such as those with dehydration, severe infection, shock, sepsis, acute heart failure, respiratory failure or hepatic impairment, or those who have recently had a myocardial infarction.

It is apparent, however, that many diabetologists and nephrologists use metformin outside of these somewhat conflicting recommendations. This guideline aims to give practical advice on the best way to use this drug, in light of this rare associated complication (now termed metformin-associated lactic acidosis (MALA)) and it suggests that in most patients *the benefits of metformin greatly outweigh the risks of serious complications.*

Benefits of metformin therapy in patients with diabetes

Metformin has achieved a strong evidence base for improving outcomes in patients with type 2 diabetes. Metformin reduces glucose levels, resulting in an average fall in HbA1c of around 10 mmol/mol (1%) within 4–6 weeks of commencing therapy. In the UK Prospective Diabetes Study (UKPDS), the use of metformin at the diagnosis of type 2 diabetes resulted in relative risk reductions of 32% for any diabetes-related endpoint; 42% for diabetes-related death; and 36% for all-cause mortality compared with diet alone. These effects were maintained for 10 years, despite glycaemic control converging within 1 year of follow-up between the initially randomly assigned groups.^{91,92} In the UKPDS, 10 patients needed to be treated with metformin (with an average fall in HbA1c of 0.9% (8–9 mmol/mol)) for 10 years in order to prevent one diabetes-related endpoint.

Vascular risks in patients with CKD and diabetes

It is now recognised that upwards of 10% of the population are affected by CKD, defined as a reduced GFR (<60 mL/min/1.73 m²) or the presence of abnormalities such as albuminuria or structural kidney problems. There is evidence that up to half of those with diabetes either have reduced GFR (<60 mL/min/1.73 m²) or albuminuria, and thus they are at risk of experiencing a further decline in GFR over time. Excess vascular disease is the main risk if a patient has diabetes, and this is further increased if a patient has CKD. Therefore diabetes control is important to reduce this risk alongside smoking cessation, and blood pressure and cholesterol control. Metformin may have an important role to play in reducing this risk.

Metformin therapy and vitamin B₁₂ deficiency in patients with CKD

Vitamin B₁₂ deficiency may be common in patients with diabetes and CKD, and malabsorption of B₁₂ with metformin has been considered to be one of the explanations for this finding.^{93,94} Although patients with peripheral neuropathy might be especially likely to have B₁₂ deficiency, the impact of this deficiency in patients with diabetic nephropathy (DN)-CKD who are on metformin has not been ascertained and requires further evaluation.

What is lactic acidosis?

Lactic acidosis is a rare systemic disorder that is diagnosed on biochemical testing with evidence of an elevated lactate level and a metabolic acidosis (a fall in serum bicarbonate, usually <15 mmol/L, on a routine electrolyte test or a fall in pH on a blood gas sample). Lactic acidosis is very rare, with an estimated prevalence of 1–5 cases per 100,000 population.⁹⁵ It has, however, a reported mortality of 30–50%. Most cases of lactic acidosis are due to marked tissue hypoperfusion in shock (due to hypovolaemia, cardiac failure or sepsis) or during a cardiopulmonary arrest. Lactate concentrations relate to outcomes.^{96–98}

Association between lactic acidosis and metformin use

Metformin is a biguanide. The related compound phenformin was originally linked with an excess number of cases of lactic acidosis (40–64/100,000 patient-years) and deaths. Coupled with this and the fact that metformin (usual half-life 1.5–5 hours) is excreted unchanged by the kidney, its initial licence in many countries warned about its potential accumulation and lactic acidosis risk in patients with renal failure. Not surprisingly, metformin has been implicated in a number of case reports and case series, in which it has been associated with lactic acidosis. These studies, however, have been criticised because there were often other recognised causes of lactic acidosis (eg hypoxia and haemodynamic compromise). Furthermore, in some studies there was no relationship between metformin dosage and lactate levels (higher metformin concentrations were poorly correlated with the degree of lactic acidosis), and metformin levels did not relate to mortality.^{99,100}

The first large population-based study to assess this risk critically was performed in Canada in the late 1990s. Almost 12,000 individuals with metformin prescriptions were followed for a number of years, and their hospital admissions were recorded. This resulted in 22,296 person-years of exposure. The primary record review revealed only two cases with laboratory findings of elevated blood lactate levels, for an incidence rate of 9 cases per 100,000 person-years of metformin exposure. In both cases, other factors besides metformin could have contributed to the lactic acidosis.¹⁰¹ No additional cases were found on review of death registrations. Further evidence against metformin being the major cause of lactic acidosis in case series comes from a large Cochrane review of 347 comparative trials and cohort studies (including the one above), which revealed no cases of fatal or non-fatal lactic acidosis in 70,490 patient-years of metformin use or in 55,451 patient-years in the non-metformin group.¹⁰² The size of this study means that the upper estimate for the true incidence of lactic acidosis per 100,000 patient-years is no higher than 4.3 cases in the metformin group and 5.4 cases in the oral hypoglycaemic agent (OHA) group. It was recognised that, in clinical practice, standard contraindications to metformin (such as heart failure and mildly impaired renal function) are often disregarded, with 54% to 73% of patients who are on metformin having at least one standard contraindication to treatment. A more recent retrospective review of the UK Clinical Practice Research Datalink (CPRD) suggested documentation of lactic acidosis or elevated lactate concentrations was

significantly associated with an eGFR of <60 mL/min/1.73 m² (adjusted hazard ratio (HR) 6.37) with the risk further increased in users of higher doses of metformin in the preceding year (>730 mg adjusted HR 11.8 and >2 g adjusted HR 13).¹⁰³

Current consensus and many reviews of the cases and the literature suggest that metformin may be a bystander when diabetes patients present with lactic acidosis.^{104,105} Many consider that this is particularly the case for diabetes patients with CKD who are at high risk of sepsis, cardiorespiratory failure and other known causes of lactic acidosis. It is suggested that this is the reason why clinicians continue to use metformin: in one primary care based study, approximately 15% of over 4,000 patients with an eGFR of <60 mL/min/1.73 m² were receiving metformin.¹⁰⁶ The most recent dose finding and pharmacokinetic study demonstrated that with dose reductions at CKD stages 3a (1.5 g), 3b (1 g) and 4 (500 mg), metformin levels can be maintained at safe circulating levels (<5 mg/L) without hyperlactatemia substantially lower than serum levels found in patients with MALA.¹⁰⁷

Balancing the risk of MALA in patients with CKD

In summary, for most patients who have diabetes, the benefits of metformin greatly outweigh the very small lactic acidosis risk: a 30–40% reduction in cardiovascular and diabetes events versus an associative risk of lactic acidosis of a maximum 5–10 episodes per 100,000 patient-years. Even if the presence of impaired renal function increases this risk by 10- or even 100-fold, the benefits continue to outweigh the risks. The loss of glycaemic control was seen in practice in a study of metformin withdrawal in patients with CKD stages 3 and 4 (ie creatinine levels of 130–220 µmol/L) which was associated with poorer glycaemic control (despite increased OHA and insulin use) as well as more weight gain, an adverse lipid profile and higher blood pressure.¹⁰⁸ In recognising that there may be subgroups of patients who are at higher risk of lactic acidosis (not just impaired renal function), however, the following practical advice for clinicians and patients contained in [Table 4](#) is relevant and, *in general supports the ongoing use of metformin for patients with stable CKD stage 3 and for some patients with CKD stage 4, albeit with increased vigilance and dose reductions down to 1,000–500 mg/day.*

6 Pioglitazone

Recommendations

- 1 We recommend that patients with type 2 diabetes and chronic kidney disease (CKD) of all stages can be considered for treatment with pioglitazone (Grade 1B).
- 2 Pioglitazone should be avoided if there is evidence that a patient has heart failure or macular oedema (Grade 1B).
- 3 Caution is required when commencing treatment in patients who have evidence of fluid overload. These patients should be monitored for fluid retention initially after 2 weeks, and 3–6-monthly thereafter (Grade 1C).
- 4 We advise that patients with CKD who gain more than 20% of their body weight within the first 2 weeks should discontinue pioglitazone (Grade 2C).
- 5 Caution is recommended when introducing pioglitazone in patients who have an increased risk of hip fractures (Grade 1C).
- 6 Consider discontinuing pioglitazone in patients who develop hip fractures while they are on pioglitazone (Grade 1D).
- 7 Do not start pioglitazone in patients who have known bladder cancer (Grade 1B).
- 8 We suggest the discontinuation of pioglitazone in patients who have painless haematuria, until bladder cancer is excluded. This reflects the current National Institute for Health and Care Excellence (NICE) guidance on type 2 diabetes, pending any downgrading of NICE guidelines as suggested by the Association of British Clinical Diabetologists (ABCD) (Grades 2C–D).

Areas that require future research

- 1 The head-to-head comparison of pioglitazone with other oral hypoglycaemic agents, in terms of safety and efficiency, across the range of estimated glomerular filtration rates (eGFRs).
- 2 The safety and efficiency of pioglitazone in combination with sodium glucose co-transporter-2 (SGLT-2) receptor blockers. For example, the benefits of the volume-reducing effect of SGLT-2 for pioglitazone-induced fluid retention; cardiovascular risk reduction; the effect on bone fractures; and the risks of urinary tract cancers with increased exposure to high glucose concentrations.
- 3 The risk of bone fractures in patients who are on pioglitazone, in comparison with other therapies in patients who have type 2 diabetes and CKD.
- 4 The efficacy and safety of pioglitazone as a third-line oral therapy in patients with type 2 diabetes and CKD.
- 5 The efficacy and safety of pioglitazone use with background insulin in patients with type 2 diabetes.

- 6 The potential cardiovascular benefit of pioglitazone treatment in patients with type 2 diabetes and chronic heart failure, where fluid retention is controlled by diuretics.
- 7 The rate of renal function decline in patients with type 2 diabetes who are taking pioglitazone.

Audit standards

- 1 The proportion of patients with type 2 diabetes and CKD who are taking pioglitazone (with or without insulin) across the range of eGFRs.
- 2 The proportion of patients with type 2 diabetes and CKD who are attaining and sustaining the recommended target HbA1C with pioglitazone as mono, dual or triple therapy, across the range of eGFRs.
- 3 The rate of cardiovascular events in patients who are taking pioglitazone, across the range of eGFRs.
- 4 The proportion of patients with type 2 diabetes and CKD who gain more than 20% of their body weight within the first 2 weeks of pioglitazone treatment, across the range of eGFRs.
- 5 The rate of hip and other fractures among pioglitazone-treated patients who have type 2 diabetes and CKD, across the range of eGFRs.
- 6 The rate of heart failure that requires hospitalisation among pioglitazone-treated patients who have type 2 diabetes and CKD, across the range of eGFRs.

Evidence base

At present, pioglitazone is the only licensed thiazolidinedione (TZD) in the UK. According to NICE, pioglitazone can be used as a second- or a third-line treatment to lower insulin resistance and improve diabetes control in patients with type 2 diabetes.¹⁰⁹ The attractions of pioglitazone lie in the low risk of hypoglycaemia and hepatic metabolism, which abolishes the need for dose adjustment when renal function declines.¹¹⁰ Possible reasons to limit its use include fluid retention and increased risk of bone fractures, but previous concerns about association with bladder cancer have been largely dismissed.

There have been remarkably few clinical trials with pioglitazone during the past 26 years when it has been available. A Cochrane review of 22 randomised controlled trials with 6,200 patients who were assigned to pioglitazone found that it reduced HbA1C by about 1%, which is comparable with sulfonylureas and metformin, but the review found no evidence for patient-orientated outcomes.¹¹¹ The PROactive study, which randomised 2,605 patients with type 2 diabetes to pioglitazone, found that it decreased all-cause mortality, non-fatal myocardial infarction (MI) and stroke as a composite secondary outcome, when compared with a placebo (hazard ratio (HR) 0.84, 0.72–0.98; $p=0.027$).¹¹² Issues with the study design were considered to have been responsible for the lack of an effect on primary composite outcome (eg all-cause mortality, non-fatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary artery or leg arteries and amputation above the ankle). The study included individual rather than disease-driven outcomes for peripheral vascular disease (eg decision about vascular surgery or amputation). Beyond its glucose-lowering effect, pioglitazone also has a favourable effect on lipids (increasing high-

density lipoproteins (HDLs) while reducing fasting triglycerides and free fatty acids);^{113,114} blood pressure (BP) (small, but sustained reduction of systolic and diastolic BP by 7 mmHg and 5 mmHg respectively);¹¹⁵ and inflammatory mediators involved in the atherosclerotic process.¹¹⁶ This is particularly relevant to patients with CKD where cardiovascular events are the main causes of morbidity. A subgroup analysis of 506 patients from the PROactive study who had an eGFR of <60 (50 ± 8) mL/min/1.73 m² confirmed a reduction in a composite secondary outcome (all-cause mortality, MI and stroke) in the pioglitazone-treated group (HR 0.66; 95% confidence interval (CI) 0.45–0.98).¹¹⁷

More recently, a 5-year, Italian, multicentre, randomised trial of cardiovascular outcomes for pioglitazone against sulfonylureas (gliclazide or glibenclamide) as an add-on to metformin in 3,028 patients aged 50–75 years found no difference in the primary composite outcome between the groups.¹¹⁸ The primary cardiovascular composite outcome was somewhat different to the now standardly reported three-point major adverse cardiac events (MACE) scale and included: all-cause death, non-fatal MI, non-fatal stroke and urgent revascularisation. The study was terminated early due to futility, but this may have been the result of the power in a low-risk population. Unlike in the PROactive trial, cardiovascular risk in the Thiazolidinediones or Sulphonylureas and Cardiovascular Accidents Intervention Trial (TOSCA.IT) was much lower; the population was less insulin resistant; and HbA1C at the start of the study was quite well controlled (7.7%). Consequently, the event rate in TOSCA.IT was about half that observed in the PROactive trial. All patients had a serum creatinine of less than 132 μ mol/L at trial entry, and 21% had microalbuminuria. There were no differences between the groups in terms of new or worsening nephropathy or progression in microalbuminuria, or in subgroup analysis based on an eGFR of < or > 60 mL/min/1.73 m². Additional findings in TOSCA.IT included the superior durability of diabetes control in the pioglitazone-treated group (treatment failure 13% v 20%; HR 0.63; CI 0.52–0.75; $p < 0.01$) and the lower rate of severe and moderate hypoglycaemia in the pioglitazone group (severe <1% v 2%, $p < 0.01$; and moderate 10% v 32%, $p < 0.01$).^{118,119}

Pioglitazone's effect on renal function and albuminuria

TZDs lower microalbuminuria and proteinuria in animal models and CKD patients with and without diabetes.^{120–123} It can be speculated that protein leak reduction is an indirect, BP-mediated effect. In a placebo-controlled, randomised study in 1,199 patients with poorly controlled type 2 diabetes (QUARTET), pioglitazone reduced microalbuminuria by 19% when compared with metformin, even though the BP changes at the study's conclusion a year later were not significant.¹¹⁷ Whether the reduction of protein leak can be translated into a slower decline of renal function in patients with diabetic nephropathy (DN)-CKD remains to be studied.

Pioglitazone's effect in patients who are on maintenance haemodialysis

Several randomised controlled trials of pioglitazone as a single agent, or in combination with insulin / other oral antidiabetic agents, demonstrated its benefits to diabetes control, lipid profile and inflammatory markers in patients with type 2 diabetes who are on dialysis.^{124,125} In a retrospective analysis of 5,290 patients with diabetes who were on dialysis, TZDs reduced the risk of all-cause mortality by a remarkable 35% (HR 0.65 (95% CI 0.48–0.87))¹²⁶ but concomitant insulin treatment abolished the benefits of TZDs. Despite this evidence, Medicines and Healthcare products Regulatory Agency (MHRA) guidance from 2016 has not been updated to reflect it.

Areas of concern

Pioglitazone increases the odds ratio (OR) for fluid retention (OR 2.22 (1.96–2.52)), which precludes its use in patients with heart failure. Patients on pioglitazone experience weight increases of approximately 1.5 kg/m² to body mass index (BMI), and it is unclear whether this is a consequence of fluid retention only.¹¹¹ Once chronic dialysis is started, pioglitazone can be reconsidered as a treatment option because it has a beneficial effect on lipid profile and inflammatory markers.

Fluid retention has implications that are relevant to patients with diabetic retinopathy. Fong *et al* analysed data from 170,000 patients with diabetes in the Kaiser Permanente Southern California Database, and found that glitazone treatment increased the risk of macular oedema (OR 2.6; 95% CI 2.4–3.0). The association was preserved even after adjustment for diabetes control, age, insulin use and pre-existing retinopathy.¹²⁷

The ADOPT study raised an issue of the association between cortical bone fractures and rosiglitazone treatment.¹²⁸ Colhoun *et al* used the Scottish National Database to investigate the relationship between a risk of hip fracture and antidiabetic drug use, and found the risk to be significantly increased with TZDs in comparison with other antidiabetic drugs. The OR for pioglitazone was 1.18 per year of exposure (95% CI 1.09–1.28; $p=3 \times 10^{-5}$), and it did not differ between genders.¹²⁹ This is of even greater concern in patients with DN-CKD who may have renal bone disease as an additional risk factor for fractures.

Another area of concern with pioglitazone is a risk of bladder cancer, which has resulted in the reduced use of pioglitazone in clinical practice, despite there being no real evidence. The concerns are fuelled by two groups of authors. Firstly, a meta-analysis of controlled clinical trials with pioglitazone by Ferwana *et al* found an increased risk of bladder cancer in pioglitazone-treated patients (HR 1.23; 95% CI 1.09–1.39; I^2 0%).¹³⁰ Secondly, an analysis of the UK Clinical Practice Research Database (CPRD) found the bladder cancer risk to be related to the duration of treatment and cumulative dose of pioglitazone.¹³¹ A subsequent definitive study, however, on the relationship between bladder cancer and pioglitazone, based on Cohort and nested case-control analyses among patients with diabetes from the Kaiser Permanente Database,¹³² dismissed an association between bladder cancer and pioglitazone. Further reassurance came from a study that included over a million patients.¹³³ Nevertheless, the extended analysis of the CPRD in 2016 reinforced the initial findings of the same authors in 2012 and concluded that the risk of bladder cancer was a drug-effect rather than a class-effect.¹³⁴ Recent NICE guidelines that are based on outdated evidence still state the risk of bladder cancer with pioglitazone to be 1–10 in 1,000, so those guidelines need to be reviewed.¹⁰⁹ In 2016, ABCD suggested the need for NICE to undertake an evidence and recommendation review.¹³⁵

Pioglitazone is one of few oral glucose lowering agents that are currently licensed for use in patients with advanced CKD (eGFR of <30 mL/min/1.73 m²). It is cheap and efficient, and has a low risk of hypoglycaemia. It can be considered for the treatment of type 2 diabetes in patients who have CKD of all stages after the exclusion of heart failure and macular oedema, and after fracture risk has been considered. Patients should be carefully and regularly monitored for fluid retention (see [Table 4](#)).

7 Dipeptidyl peptidase-4 inhibitors

Recommendations

- 1 We recommend that patients with type 2 diabetes and chronic kidney disease (CKD) of all stages be considered for treatment with dipeptidyl peptidase-4 (DPP-4) inhibitors (Grade 1B).
- 2 We recommend that doses of all UK licensed DPP-4 inhibitors are appropriately reduced in accordance with the degree of renal impairment (including maintenance haemodialysis (MHDx)) except linagliptin (Grade 1B).
- 3 Patients with type 2 diabetes and CKD can be safely prescribed DPP-4 inhibitors without the risk of hypoglycaemia or weight gain at all stages of renal disease (Grade 1B).
- 4 There are no current data to recommend the use of DPP-4 inhibitors specifically to lower albuminuria in patients with type 2 diabetes and CKD (Grade 1C).
- 5 There are no current data to suggest that DPP-4 inhibitors (except saxagliptin) are associated with an excess risk of hospitalisation for patients with heart failure, type 2 diabetes and CKD (Grade 1A).

Areas that require further research

- 1 A head-to-head comparison of DPP-4 inhibitors with other oral hypoglycaemic agents (sulfonylureas and pioglitazone) that are licensed for use in patients with CKD, in terms of safety, efficacy, risk of hypoglycaemia, weight gain and hospitalisation for heart failure, across a wide range of eGFRs.
- 2 The efficacy and safety of the use of a DPP-4 inhibitor with background insulin in patients with type 2 diabetes.
- 3 A head-to-head comparison between various DPP-4 inhibitors with regard to HbA1c reduction in patients with type 2 diabetes and CKD.
- 4 The mechanisms that underlie the potential differential effects of DPP-4 agents on albuminuria and their relationship with glucose lowering.

Audit standards

- 1 The proportion of patients with type 2 diabetes and CKD who are taking DPP-4 inhibitors, according to the degree of renal impairment and across the ranges of estimated glomerular filtration rate (eGFR), including those who are on MHDx.
- 2 The proportion of patients with type 2 diabetes and CKD who are taking appropriate doses of DPP-4 inhibitors, according to their degree of renal impairment.
- 3 The proportion of patients with type 2 diabetes and CKD who are attaining the recommended target HbA1C with DPP-4 inhibitors as mono, dual and triple therapy, including insulin, according to their stage of CKD.
- 4 The proportion of patients with type 2 diabetes and CKD who are sustaining the recommended target HbA1C with DPP-4 inhibitors as mono, dual and triple therapy, including insulin, according to their stage of CKD.
- 5 The proportion of patients with type 2 diabetes and CKD who are taking DPP-4 inhibitors who show a percentage reduction in albuminuria.

- 6 The comparative efficacy of DPP-4 inhibitors in patients with type 2 diabetes and CKD, across the range of eGFRs.
- 7 The incidence of hospitalisation of patients with heart failure who have type 2 diabetes and CKD and are being treated with DPP-4 inhibitors.
- 8 The efficacy of glycaemic control (HbA1c reduction) with reduced doses of DPP-4 inhibitors in patients with progressive renal impairment.

Areas of concern

- 1 The potential for heart failure in patients who have a high cardiovascular risk and CKD who are using DPP-4 inhibitors.

Introduction

DPP-4 inhibitors bind selectively to DPP-4 and prevent the rapid hydrolysis of glucagon-like peptide 1 (GLP-1). They have a modest glucose-lowering effect, compared with other oral hypoglycaemic agents. DPP-4 inhibitors are known to have a very low risk of leading to hypoglycaemia and are generally associated with a favourable safety and tolerability profile. Placebo-controlled studies with linagliptin, vildagliptin, saxagliptin and sitagliptin, as well as a recent pooled analysis with linagliptin, have underscored the likely positive benefit–risk profile of DPP-4 inhibitors in patients with type 2 diabetes and mild-to-severe renal impairment.^{136–141}

Sitagliptin

Sitagliptin undergoes minimal metabolism, mainly by the cytochrome P450 isoenzyme (CYP3A4) and to a lesser extent by CYP2C8. About 79% of a dose is excreted unchanged in the urine. Renal excretion of sitagliptin involves active tubular secretion; it is a substrate for organic anion transporter-3 and P-glycoprotein.

When considering the use of sitagliptin in combination with another anti-diabetic medicinal product, the conditions for its use in patients with renal impairment should be checked. Dose adjustment is based on renal function, so it is recommended that renal function is assessed prior to the initiation of sitagliptin, and ongoing (routine annual or biannual) monitoring of GFR may determine the need for dosage reduction.

Most trials that involve the use of sitagliptin in patients with varying degrees of renal failure (including dialysis) have compared its safety, efficacy and effect on renal function against a sulfonylurea. Relative to glipizide (the most common sulfonylurea comparator), sitagliptin was generally well-tolerated, and had a lower risk of hypoglycaemia and weight gain. It also provided similar glycaemic efficacy when its dose was adjusted according to a patient's degree of renal impairment.^{142–144}

For patients with mild renal impairment (creatinine clearance (CrCl) of ≥ 50 mL/min), no dose adjustment is required. For patients with moderate renal impairment (CrCl of ≥ 30 to < 50 mL/min), the dosage of sitagliptin is 50 mg once daily.

DPP-4 inhibitors are one of the few therapies that have clear licensing in haemodialysis and clear recommendations. Sitagliptin is not removed by conventional dialysis but it is removed by high-flux dialysis: in total, 13.5% of the drug is removed by a 3–4 hour dialysis session.¹⁴³ For patients with severe renal impairment (CrCl of < 30 mL/min) or with end-stage renal

disease (ESRD) who require haemodialysis or peritoneal dialysis, the dosage of sitagliptin is 25 mg once daily. Treatment may be administered without regard to the timing of dialysis.

In a study performed with sitagliptin by Harashima *et al*,¹⁴⁵ albuminuria was a secondary endpoint in 82 subjects who were enrolled to the 52-week, prospective, single-arm study where sitagliptin was added to sulfonylureas (glimepiride or gliclazide) with or without metformin. The primary endpoint was a change in HbA1c. After 52 weeks, sitagliptin treatment reduced HbA1c by 0.8% and reduced the urine albumin:creatinine ratio (UACR) from 76.2 ± 95.6 to 33.0 ± 48.1 mg/g, along with a slight decreases in body mass index (BMI) and blood pressure (BP).

To evaluate CKD and cardiovascular outcomes, the Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS) studied 14,671 participants with type 2 diabetes and cardiovascular disease who were treated with sitagliptin or a placebo (according to a baseline estimated glomerular filtration rate (eGFR)).¹⁴⁶ Cardiovascular and CKD outcomes were evaluated over a median of 3 years, with participants' baseline being categorised as eGFR stages 1, 2, 3a, and 3b (≥ 90 , 60–89, 45–59 or 30–44 mL/min/1.73 m² respectively).

Sitagliptin therapy was not associated with increased risk of major adverse cardiovascular outcomes for any eGFR stage ($p > 0.44$). Kidney function declined at the same rate in both treatment groups, with a marginally lower but constant eGFR difference (-1.3 mL/min/1.73 m²) in participants who were assigned to take sitagliptin. Impaired kidney function is associated with worse cardiovascular outcomes. Sitagliptin, however, has no clinically significant impact on cardiovascular or CKD outcomes, irrespective of a patient's baseline eGFR. In the subset of participants who had UACR data, the median value was marginally and consistently lower in the sitagliptin group compared with the placebo group, with an estimated overall mean difference of -0.18 mg/g (95% confidence interval (CI) -0.35 to -0.02 ; $p = 0.031$). The 4-year UACR differences between the treatment groups were similar for each eGFR stage, with no significant interactions of treatment effect by eGFR stage. In the 26% of TECOS participants for whom UACR data were available, the mean UACR values were marginally lower in the sitagliptin group than in the placebo group. It is uncertain whether these small offsets in eGFR and UACR would have any long-term clinical implications.

Linagliptin

Linagliptin has minimal metabolism to inactive metabolites. Approximately 80% is eliminated in the faeces and 5% in the urine. It is not removed by dialysis. In moderate renal failure, a moderate increase in exposure of about 1.7-fold was observed compared with a control group. Exposure in patients with type 2 diabetes and severe renal failure was increased by about 1.4-fold compared with patients with type 2 diabetes and normal renal function. Steady-state predictions for the area under the curve (AUC) of linagliptin in patients with ESRD indicated an exposure that is comparable with that of patients with moderate or severe renal impairment. No dose adjustment is required and linagliptin at a dosage of 5 mg per day may be used in patients who are on MHDx.¹⁴⁷

Linagliptin pharmacokinetics was studied under single-dose and steady-state conditions in subjects with mild, moderate and severe renal impairment. The accumulation half-life of linagliptin ranged from 14–15 hours in subjects with normal renal function, to 18 hours in those with severe renal impairment. Renal impairment only had a minor effect on linagliptin pharmacokinetics and thus there was no need to adjust the linagliptin dose in renally impaired patients with type 2 diabetes.¹⁴⁸

In another trial,¹⁴⁹ treatment with linagliptin or a placebo followed by glimepiride was studied in patients with type 2 diabetes and moderate to severe renal impairment. The

study found that such treatment produced beneficial changes in glycaemic control with an acceptable side-effect profile that did not have any effect on renal function.

In patients with type 2 diabetes and severe renal impairment, linagliptin provided clinically meaningful improvements in glycaemic control with a very low risk of severe hypoglycaemia, stable body weight and no cases of drug-related renal failure.¹⁴⁰

Albuminuria reduction with linagliptin was studied in a randomised, double-blind, placebo-controlled trial (duration 24–52 weeks) in 2012.¹⁵⁰ The inclusion criteria were: persistent albuminuria (defined as UACR 30–3,000 mg/g) and stable treatment with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) at baseline. Overall, 168 patients were treated with linagliptin and 59 patients were in a placebo group. The placebo-corrected reduction of HbA1c reached –0.71%, while BP and renal function remained unchanged. In the linagliptin-treated group, the UACR significantly decreased by 33%, with a between-group difference versus the placebo of –29%. This did not correlate with the magnitude of HbA1c change, which suggests that the albuminuria reduction effects may be independent of the improvement in glycaemic control.

Another, larger meta-analysis of 13 linagliptin trials, which included 5,466 patients, focused on composite renal outcomes. The analysis revealed a hazard ratio (HR) of 0.84 in favour of linagliptin compared with a placebo or comparator.¹⁵¹ The risk ratios (RRs) were 0.85 for microalbuminuria and 0.88 for macroalbuminuria. These studies were not primary outcome studies to test the effect of linagliptin on microalbuminuria and renal function; however, they indicate its possible nephroprotective effects.

A pooled analysis of four randomised, double-blind, placebo-controlled clinical trials found that when linagliptin was administered with background renin-angiotensin-aldosterone system (RAAS) inhibition, it significantly reduced albuminuria by 28% after 24 weeks of treatment.¹⁵²

The ongoing Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus (CARMELINA), a study of patients who are at high vascular risk, is due to report in early 2018.¹⁵³ It will hopefully not only provide cardiovascular safety data but also data about the time to first occurrence of some adjudicated composite renal endpoints.

Vildagliptin

About 69% of a dose of vildagliptin is metabolised, mainly by hydrolysis in the kidneys to inactive metabolites. About 85% of a dose is excreted in the urine (23% as unchanged drug) and 15% is excreted in the faeces. On average, vildagliptin's AUC increased by 1.4-, 1.7- and two-fold in patients with mild, moderate and severe renal impairment, respectively, compared with healthy subjects. The AUC of the metabolites LAY151 (the main metabolite) and BQS867 increased on average by about 1.5-, three- and seven-fold in patients with mild, moderate and severe renal impairment, respectively. LAY151 concentrations were approximately two- to three-fold higher than in patients with severe renal impairment.¹⁵⁴

In a randomised clinical trial of vildagliptin and sitagliptin in patients with type 2 diabetes and severe renal impairment (eGFR of <30 mL/min/1.73 m²), vildagliptin 50 mg once daily and sitagliptin 25 mg once daily demonstrated similar efficacy, and both drugs were well-tolerated with no effect on renal function.¹⁵⁵

Vildagliptin is not removed by conventional dialysis, but it is removed by high-flux dialysis. After a 3–4-hour haemodialysis session, 3% of vildagliptin is removed. The main metabolite (LAY151) is also removed by haemodialysis.

No dose adjustment is required in patients with mild renal impairment (CrCl of ≥ 50 mL/min). In patients with moderate or severe renal impairment or those with ESRD, the recommended dosage is 50 mg once daily.

A retrospective meta-analysis of prospectively adjudicated cardiovascular events that involved 17,446 patients from 40 double-blind, randomised controlled phase III and IV vildagliptin studies revealed that a major adverse cardiac event (MACE) occurred in 83 (0.86%) vildagliptin-treated patients and 85 (1.20%) comparator-treated patients, with an HR of 0.82 (95% CI 0.61–1.11). Confirmed heart failure events were reported in 41 (0.43%) vildagliptin-treated patients and 32 (0.45%) comparator-treated patients, with an HR of 1.08 (95% CI 0.68–1.70).

This large meta-analysis thus indicates that vildagliptin is not associated with an increased risk of cardiovascular events or heart failure in high-risk diabetes patients, such as those with congestive heart failure and/or moderate or severe renal impairment.¹⁵⁶

Alogliptin

The efficacy and safety of the recommended doses of alogliptin was investigated separately in a subgroup of patients with type 2 diabetes and severe renal impairment / ESRD in a placebo-controlled study (59 patients were on alogliptin and 56 patients were on a placebo for 6 months). Alogliptin use in the subgroup was found to be consistent with the profile obtained in patients with normal renal function. Furthermore, the pharmacokinetic profile of a single dose of alogliptin was evaluated in patients with renal impairment and in healthy volunteers.¹⁵⁷ Compared with healthy volunteers, an approximate 1.7-fold increase ($p=0.002$) in the alogliptin total plasma AUC was observed in patients with mild renal impairment. In patients with moderate and severe renal impairment and ESRD, the alogliptin total plasma exposure increased by 2.1-fold ($p<0.001$), 3.2-fold ($p<0.001$) and 3.8-fold ($p<0.001$) respectively, compared with healthy volunteers. The authors concluded that a single oral 50 mg dose of alogliptin was generally well-tolerated in all groups, and that no dose adjustment is necessary for patients with mild renal impairment (CrCl of >50 to ≤ 80 mL/min). In those with moderate renal impairment (CrCl of ≥ 30 to ≤ 50 mL/min), the alogliptin dosage should be reduced to 25 mg once daily. In patients with severe renal impairment (CrCl of <30 mL/min) including ESRD, the dosage should be reduced to 12.5 mg once daily. Fujii *et al*¹⁵⁸ evaluated the efficacy and safety of alogliptin 6.25 mg once daily in 30 patients with type 2 diabetes who were undergoing haemodialysis over a 48-week period in an open label study. It concluded that alogliptin improved glycaemic control and was generally well-tolerated in patients. Alogliptin may be administered without regard to the timing of dialysis.

EXAMINE was a cardiovascular safety trial that evaluated alogliptin versus a placebo on top of the standard of care therapy in 5,380 patients with recent acute coronary syndrome (ACS) (15–90 days prior to their study entry) for up to 40 months. The median study duration was 18 months. The patients' baseline characteristics were balanced in both groups (age 61 years; 68% male; 71% with an eGFR of ≥ 60 mL/min/1.73 m²). Compared with the placebo, alogliptin did not significantly affect rates of CKD progression, albuminuria change or dialysis initiation. In follow-up, the changes in the renal laboratory parameters for the group who were on alogliptin were comparable to that of the placebo group.¹⁵⁹ Post-hoc analysis of the EXAMINE study showed that, although there was a sign of excess heart failure in the alogliptin group in patients who had no heart failure prior to randomisation (HR 1.76; CI 1.07–2.90; $p=0.026$), there was no overall difference in the proportion of patients who were hospitalised for heart failure between the alogliptin group (2.9%) and the placebo group

(3.3%) (HR 1.19; 95% CI 0.90–1.58; $p=0.22$). The composite outcome of hospitalisation for heart failure and cardiovascular death was similar in the alogliptin group (3.1%) and the placebo group (2.9%) (HR 1.07; 95% CI 0.79–1.46). EXAMINE trial analysis showed that alogliptin does not increase heart failure morbidity or mortality in patients with type 2 diabetes or recent ACS, or worsen heart failure outcomes in patients with pre-existing heart failure.

Saxagliptin

A single-dose, open-label study¹⁶⁰ was conducted to evaluate the pharmacokinetics of a 10 mg oral dose of saxagliptin in subjects with varying degrees of chronic renal impairment, compared with subjects with normal renal function. The study included patients with renal impairment, classified on the basis of CrCl (based on the Cockcroft–Gault formula) as being mild (>50 to ≤ 80 mL/min), moderate (≥ 30 to ≤ 50 mL/min) or severe (<30 mL/min), as well as patients with ESRD who were on haemodialysis.

The degree of renal impairment did not affect the C_{max} (the maximum serum concentration that a drug achieves after it has been administered) of saxagliptin or its major metabolite. In subjects with mild renal impairment, the mean AUC values of saxagliptin and its major metabolite were 1.2- and 1.7-fold higher, respectively, than the mean AUC values in subjects with normal renal function. Because increases of this magnitude are not clinically relevant, dose adjustment in patients with mild renal impairment is not recommended.

In subjects with moderate or severe renal impairment or in subjects with ESRD who are on haemodialysis, the AUC values of saxagliptin and its major metabolite were up to 2.1- and 4.5-fold higher, respectively, than AUC values in subjects with normal renal function. The dosage should be reduced to 2.5 mg once daily in patients with moderate or severe renal impairment. Data on the experience of patients with severe renal impairment are very limited. Therefore, saxagliptin should be used with caution in this population. Saxagliptin is not recommended for patients with ESRD who require haemodialysis.

In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53 trial (SAVOR-TIMI 53), patients with type 2 diabetes who are at risk of cardiovascular events were stratified according to their baseline renal function. The primary endpoint was cardiovascular death, myocardial infarction (MI) or ischemic stroke. After a median duration of 2 years, saxagliptin neither increased nor decreased the risk of the primary and secondary composite endpoints compared with the placebo, irrespective of the patients' renal function. Patients with renal impairment achieved reductions in microalbuminuria with saxagliptin ($p=0.041$) that were similar to those of the overall trial population. The risk of either the development or progression of microalbuminuria was significantly reduced with saxagliptin at a median follow-up period of 2.1 years in the long-term SAVOR-TIMI 53 phase 4 clinical trial.¹⁶¹ Thus saxagliptin reduced progressive albuminuria, irrespective of the baseline renal function in those with and without albuminuria at baseline, and without an adverse impact on eGFR.¹⁶² The rate of hospitalisation for heart failure was 289 (3.5%) in the saxagliptin group versus 228 (2.8%) in the placebo group (HR 1.27; 95% CI 1.07–1.51; $p=0.007$). This represented a 27% increase in the relative risk of hospitalisation for heart failure in the saxagliptin group, which again was similar irrespective of the patients' degree of renal disease.¹⁶³

In the SAVOR-TIMI 53 trial, hospitalisation for heart failure was a predefined component of the secondary endpoint. The baseline N-terminal prohormone of brain natriuretic peptide (NT-proBNP) was measured in 12,301 patients. More patients who were treated with saxagliptin (289, 3.5%) were hospitalised for heart failure, compared with the placebo (228,

2.8%) (HR 1.27; 95% CI 1.07–1.51; $p=0.007$). Corresponding rates at 12-months were 1.9% versus 1.3% (HR 1.46; 95% CI 1.15–1.88; $p=0.002$), with no significant difference thereafter (time-varying interaction $p=0.017$). There were 741 hospitalisations for heart failure in 517 patients across both the treatment groups in the SAVOR-TIMI 53 trial. The rates of hospitalisation for heart failure were 1.1% in the saxagliptin group and 0.6% in the control group (HR 1.80; 95% CI 1.29–2.55; $p=0.001$) at 6 months, and 1.9% and 1.3% respectively at 12 months (HR 1.46; 95% CI 1.15–1.88; $p=0.002$). The risk of hospitalisation for heart failure with saxagliptin subsided at 10–11 months after randomisation. The risk of re-hospitalisation for heart failure was similar in both treatment groups. Multivariate analysis of the SAVOR-TIMI 53 trial showed that hospitalisation for heart failure was strongly associated with prior heart failure, or elevated baseline levels of proBNP. The initial suggestion that baseline eGFR was also associated with heart failure was not verified in the subsequent adjusted analyses by different ranges of eGFR.^{161,163} Thus, although no increase in cardiovascular events was reported, the SAVOR-TIMI 53 trial had unexpected heart failure which was significantly increased by 27%.

8 Sodium glucose co-transporter-2 inhibitors

Recommendations

- 1 Sodium glucose co-transporter-2 (SGLT-2) inhibitors are currently licensed for the treatment of type 2 diabetes only when the estimated glomerular filtration rate (eGFR) is >60 mL/min/1.73 m². For dapagliflozin, the drug should be withheld when a patient's eGFR falls below this level, while canagliflozin and empagliflozin may be continued until the eGFR falls below 45 mL/min/1.73 m² (albeit at their lower licensed doses). We support these recommendations (Grade 1B).
- 2 There is clinical trial evidence that empagliflozin and canagliflozin reduce cardiovascular outcomes in patients with type 2 diabetes who are at high cardiovascular risk (Grade 1A). Subgroup analysis of these trials suggests that patients with an eGFR of 60 to <90 mL/min/1.73 m² gain cardiovascular benefit, so we recommend that this drug class be considered over other glucose-lowering therapies for patients with stage 2 chronic kidney disease (CKD) (Grade 2B).
- 3 Pre-specified analyses of the same trials examined renal endpoints and showed the benefit of SGLT-2 inhibition for hard endpoints, such as changes in serum creatinine (and eGFR) and the need for end-stage renal replacement therapy. SGLT-2 inhibitors (currently empagliflozin and canagliflozin) are recommended for renoprotection for patients who have type 2 diabetes and are at high cardiovascular risk (Grade 1A).
- 4 Patients with type 2 diabetes and CKD who are treated with SGLT-2 inhibitors need only perform frequent self-monitoring of blood glucose when they are also being treated with agents that can cause hypoglycaemia (such as sulfonylureas and insulins) (Grade 1A).

Areas that require future research

- 1 The beneficial renal effects (seen as secondary endpoints) of empagliflozin and canagliflozin, observed down to an eGFR of 30 mL/min/1.73 m² (ie CKD stage 3) need to be confirmed in studies with primary renal endpoints. This may ultimately lead to a change in the licence indication for SGLT-2 inhibitors.
- 2 Research needs to establish whether the cardiovascular benefits of empagliflozin and canagliflozin also extend to patient with type 2 diabetes who have an eGFR of <30 mL/min/1.73 m², where the glycaemic effect of these agents is minimal.
- 3 The beneficial cardiovascular effects of empagliflozin and canagliflozin need to be confirmed for other members of the SGLT-2 inhibitor class.
- 4 Studies need to examine the cardiovascular and renal effects of SGLT-2 inhibitors in patients with type 2 diabetes who are at lower cardiovascular risk (who make up the majority of patients with type 2 diabetes)
- 5 Trials need to investigate whether the renal and cardiovascular benefits of SGLT-2 inhibitors are seen in patients with pre-diabetes and in the population who do not have diabetes.

- 6 The long-term impact of SGLT-2 inhibitors on metabolic bone disease, and parameters such as calcium, phosphate and magnesium should be investigated.

Evidence base

The hypoglycaemic mechanism action of SGLT-2 inhibitors is to inhibit the reabsorption of glucose that has been filtered by the glomeruli in the kidneys.¹⁶⁴ For this reason, their glucose-lowering is limited by declining renal function (since the amount of filtered glucose is reduced) and so the licences of SGLT-2 inhibitors have been adapted accordingly. In 2018, there are three licensed SGLT-2 inhibitors in the UK (dapagliflozin, canagliflozin and empagliflozin) and none of these are recommended for initiation when a patient's eGFR is <60 mL/min/1.73 m² (ie CKD stage 3). Dapagliflozin should be withheld when a patient's eGFR falls below this level (having being initiated above 60 mL/min/1.73 m²), while canagliflozin and empagliflozin should only be used at their lower doses in patients with CKD stage 3a and then should be withdrawn when the eGFR falls below 45 mL/min/1.73 m².^{165–167}

There has been a presumption that the reduction in HbA1c achieved by the SGLT-2 inhibitor class, along with secondary effects of weight loss and a fall in systolic blood pressure (BP), may manifest as a renal benefit in patients with type 2 diabetes. There has also, however, been concern that drugs that primarily affect the kidneys (not previously a target for glucose lowering) could be harmful, despite the lack of adverse effects seen in (the very rare cases of) benign familial glucosuria, where SGLT-2 activity is diminished.¹⁶⁸

Post-marketing reports from the US Food and Drug Administration (FDA) Adverse Event Reporting System have identified a potential signal for acute kidney injury (AKI) with all approved SGLT-2 inhibitors.¹⁶⁹ This may reflect the initial decline in eGFR due to the known renal haemodynamic effects of SGLT-2 inhibition.¹⁷⁰ In contrast, the two large cardiovascular outcome trials for empagliflozin and canagliflozin have both shown evidence for renoprotection, and this was seen in subjects who had an eGFR of 30–60 mL/min/1.73 m²: patients in whom SGLT-2 inhibitors would currently not be initiated.^{171,172} These findings are discussed in more detail later in this chapter. In addition, a recent propensity matched retrospective review of SGLT-2 inhibitor use did not suggest any increased risk of AKI.¹⁷³

A meta-analysis of randomised clinical trials has shown that SGLT-2 inhibitors marginally increase serum magnesium levels in type 2 diabetes patients, which appears to be a drug-class effect.¹⁷⁴ Further investigations are required to examine the clinical significance of elevated magnesium levels in individuals with type 2 diabetes.

Adverse events that have been attributed to the SGLT-2 inhibitor class include the following.

Genital mycotic infection

This is a class effect that is presumed to be consequent upon glucosuria. It is more frequent in women than men, and is often seen early after treatment is initiated. It typically responds to over-the-counter medication, although some patients have recurrent episodes that require withdrawal of the SGLT-2 inhibitor.¹⁷⁵

Urinary tract infection

While in some studies there has been a signal for increased urinary tract infection (UTI) in patients who receive an SGLT-2 inhibitor, this is not a consistent finding and there is still uncertainty about whether this is a true side effect of the drug class.¹⁷⁶ An increased risk of urosepsis has not been reported.

Diabetic ketoacidosis

Warnings about diabetic ketoacidosis (DKA) in patients who are receiving SGLT-2 inhibitors have been issued by both the FDA and the European Medicines Agency (EMA).^{177,178} Proposed mechanisms include increased ketone body uptake by the kidneys (consequent on increased sodium delivery to the distal tubule) and a shift from carbohydrate to fat metabolism due to changes in the insulin:glucagon ratio (glucagon levels rise with SGLT-2 inhibition).¹⁷⁹ Although there was an initial bias towards a diagnosis of 'euglycaemic DKA', the majority of cases appear to be associated with significant hyperglycaemia. Some of the reported cases were undoubtedly patients with type 1 diabetes and latent autoimmune diabetes in adult-life (LADA), for whom the drug class is not currently licensed. Other common features were large reductions of insulin dose and established precipitants of DKA, such as dehydration, infection and surgery. It is of note that post-hoc analyses of the clinical trial programmes of the three SGLT-2 inhibitors have shown little evidence of a safety signal for DKA. Nevertheless 'sick day rules' ([Appendix B](#)) should be recommended, with temporary drug cessation.

Increased risk of bone fracture

A warning regarding bone fractures was included in the US label for canagliflozin when it was launched, and this was strengthened in September 2015.¹⁸⁰ A study subsequently confirmed a reduction in bone mineral density in patients who receive canagliflozin, and a meta-analysis reported that fracture risk was increased in canagliflozin-treated patients.^{181,182} The Canagliflozin Cardiovascular Assessment (CANVAS) study has subsequently confirmed a significant increase in fractures in patients who receive canagliflozin.¹⁷² This signal has not been seen with dapagliflozin or empagliflozin.

Amputation

The FDA issued a warning in 2016, following an interim safety analysis of the CANVAS study of canagliflozin.¹⁸³ The full CANVAS study confirmed a significant increase in amputations, with an elevated hazard ratio (HR) for both minor (toe and transmetatarsal) and major (ankle, above- and below-knee) surgery.¹⁷² This has led to a further FDA safety announcement.¹⁸⁴ To date, an increased risk of amputation has not been reported with either dapagliflozin or empagliflozin.

Empagliflozin

Empagliflozin was the first of the oral hypoglycaemic agents to show superiority over a placebo in the era of modern cardiovascular outcome trials (CVOTs) in type 2 diabetes. In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME) study, 7,020 patients were randomly assigned to receive empagliflozin 10 mg or 25 mg once per day or a placebo, and they remained under observation for a median of 3.1 years.¹⁷¹ The primary outcome of death from cardiovascular causes, non-fatal myocardial infarction (MI) and non-fatal stroke (three-point major adverse cardiac events (MACE) end-point) occurred in 490 out of 4,687 patients (10.5%) in the pooled empagliflozin group and in 282 out of 2,333 patients (12.1%) in the placebo group. This gave an HR in the empagliflozin group of 0.86, with a 95% confidence interval (CI) (0.74–0.99); the p-value of 0.04 confirmed superiority over the placebo.

The result was largely driven by the significantly lower rate of death from cardiovascular causes in the empagliflozin group (3.7% versus 5.9% in the placebo group; 38% relative risk reduction (RRR)), but hospitalisation for heart failure (2.7% and 4.1%, respectively; 35% RRR) and death from any cause (5.7% and 8.3%, respectively; 32% (RRR)) were also significantly

reduced. It was of great interest that all of these beneficial effects emerged after only a few months of trial observation.

A subgroup analysis of the three-point MACE, according to baseline eGFR, showed heterogeneity, albeit non-significant. The subgroup of patients with an eGFR of 60–90 mL/min/1.73 m² had a significantly lower event rate for the primary endpoint, while those with an eGFR of <60 mL/min/1.73 m² had a similar reduction in the point estimate, but this was not significant (due to the lower number of subjects in this cohort). Trial subjects with an eGFR of >90 mL/min/1.73 m² showed no evidence of primary endpoint reduction, which is consistent with a hypothesis that only the patients with the highest risk of cardiovascular events gain a benefit from SGLT-2 inhibition.

Pre-specified secondary analyses of renal outcomes from the EMPA-REG OUTCOME trial have subsequently been published.¹⁸⁵ The composite renal outcome was made up of four endpoints: macroalbuminuria; doubling of serum creatinine with an eGFR of ≤45 mL/min/1.73 m²; time to first initiation of continuous renal replacement therapy; and renal death. The latter three outcomes are clearly clinically relevant renal endpoints and were analysed as a composite of 'hard renal outcomes'. This composite was reduced by 46% (HR 0.54; CI 0.40–0.75; p<0.001)¹⁸⁵ and all of the individual renal outcomes were reduced in the empagliflozin groups.

Although it is generally regarded to be a less important renal outcome, an exploratory analysis of urinary albumin:creatinine ratio (UACR) in the EMPA-REG OUTCOME trial has been published.¹⁸⁶ After 12 weeks, the placebo-adjusted geometric mean ratio of UACR change from baseline with empagliflozin was –7% (95% CI –12 to –2; p=0.013) in patients with normoalbuminuria; –25% (–31 to –19; p<0.0001) in patients with microalbuminuria; and –32% (–41 to –23; p<0.0001) in patients with macroalbuminuria. These reductions were maintained at 164 weeks and remained significant after cessation of treatment for those with baseline microalbuminuria and macroalbuminuria. Patients who received empagliflozin were also more likely to experience a sustained improvement from microalbuminuria to normoalbuminuria (HR 1.43; 95% CI 1.22 to 1.67; p<0.0001) and from macroalbuminuria to microalbuminuria or normoalbuminuria (HR 1.82; CI 1.40–2.37; p<0.0001).

Canagliflozin

Renal-related adverse events with canagliflozin were reported from a pooled analysis of seven active- and placebo-controlled trials (n=5,598) and a 104-week study versus glimepiride (n=1,450).¹⁸⁷ Overall, the incidence of renal adverse events was low and similar in canagliflozin and non-canagliflozin treated groups. In a study versus glimepiride,¹⁸⁸ the incidence of renal-related adverse events with canagliflozin was generally stable over time, while the incidence with glimepiride increased over 104 weeks.

Heerspink *et al*¹⁸⁹ performed a secondary analysis of the same clinical trial of patients who were randomly assigned to either canagliflozin 100 mg once per day, canagliflozin 300 mg once per day or glimepiride up-titrated to 6–8 mg once per day.¹⁸⁸ The endpoints were an annual change in albuminuria and eGFR over the 2 years of follow-up. The canagliflozin 100 mg and canagliflozin 300 mg groups had eGFR reductions of 0.5 mL/min/1.73 m² (95% CI 0.0–1.0) and 0.9 mL/min/1.73 m² per year (95% CI 0.4–1.4) versus 3.3 mL/min/1.73 m² per year (95% CI 2.8–3.8) for glimepiride (p=0.01 for each canagliflozin comparison). In the subgroup of patients with a baseline urinary albumin:creatinine ratio of >30 mg/g, urinary albumin:creatinine ratio decreased more with canagliflozin 100 mg (31.7%; 95% CI 8.6%–48.9%; p=0.01) and canagliflozin 300 mg (49.3%; 95% CI 31.9%–62.2%; p=0.001) compared with glimepiride. It is noteworthy that the three cohorts had similar reductions in HbA1c at

both the 1-year and 2-year observation points, which implies that any renal benefits were independent of glucose lowering.

The CANVAS Program integrated data from two trials that involved a total of 10,142 participants with type 2 diabetes and a high cardiovascular risk.¹⁷² The participants in each trial were randomly assigned to receive canagliflozin or a placebo, and they were followed for a mean of 188.2 weeks. The primary outcome was a composite of death from cardiovascular causes, non-fatal myocardial infarction (MI), or a non-fatal stroke (the same three-point MACE that was assessed in the EMPA-REG OUTCOME study). The mean age of the participants was 63.3 years; 35.8% were women; the mean duration of diabetes was 13.5 years; and 65.6% had a history of cardiovascular disease. The rate of the primary outcome was lower with canagliflozin (occurring in 26.9 versus 31.5 participants per 1,000 patient-years; HR 0.86; 95% CI 0.75–0.97; $p < 0.001$ for non-inferiority; $p = 0.02$ for superiority).

Although on the basis of the pre-specified hypothesis testing sequence the renal outcomes were not reported as being statistically significant, the results showed a benefit from canagliflozin with respect to the progression of albuminuria (HR 0.73; 95% CI 0.67–0.79) and the composite outcome of a sustained 40% reduction in the eGFR; a need for renal-replacement therapy; or death from renal causes (HR 0.60; 95% CI 0.47–0.77).

Dapagliflozin

Twelve double-blind, placebo-controlled, randomised clinical trials that included 4,545 subjects were analysed up to 24 weeks.¹⁹⁰ Six of the studies also included longer-term data (up to 102 weeks ($n = 3,036$ subjects)). Patients with type 2 diabetes with normal or mildly impaired renal function (eGFR of 60–90 mL/min/1.73 m²) were treated with dapagliflozin (2.5 mg, 5 mg or 10 mg per day) versus a placebo.

The mean eGFR showed small transient reductions with dapagliflozin at week 1, but this returned to near baseline values by week 24, and thereafter was stable to week 102. Mean eGFR changes were similar for each dapagliflozin dose throughout the observation period. Renal adverse events were similar in frequency to the placebo through 24 weeks (1.4%, 1.3%, 0.9% and 0.9%) and 102 weeks (2.4%, 1.8%, 1.9% and 1.7%, respectively) and few events were serious (between 0.1% and 0.3%). The most common renal adverse event was an increase in serum creatinine, which occurred equally in the dapagliflozin and placebo groups. Small increases from baseline in mean urea and serum albumin levels were observed with dapagliflozin versus the placebo at week 102, which was consistent with its mild osmotic diuretic effect. The moderate renal impairment subgroup (eGFR of 30–60 mL/min/1.73 m²) had the highest proportion of patients with renal adverse events up to 24 weeks and, in this subgroup only, renal adverse events were more common in dapagliflozin-treated patients than those in the placebo group, but with no dose dependence.

One publication and several abstracts have reported on the effect of dapagliflozin on the surrogate renal endpoint of change in UACR.¹⁹¹ These are post-hoc analyses of pooled data from phase III clinical trials and they show a reduction in albuminuria that appears to be independent of changes in HbA1c, blood pressure (BP), body weight and eGFR. No studies have assessed hard renal endpoints, such as a doubling of serum creatinine or progression to end-stage renal disease (ESRD).

Future prospects

The cardiovascular and renal benefits seen with empagliflozin in the EMPA-REG OUTCOME study were largely unexpected, and replication of these results for canagliflozin is very encouraging for the SGLT-2 inhibitor class. There is also supportive evidence of cardiovascular benefit for dapagliflozin from real-world database analyses, although the formal CVOT (DECLARE-TIMI 58) will not report until 2019.^{192–194} In the meantime, the licence for empagliflozin has been changed in both the US and Europe, in order to acknowledge the additional benefits in patients with high cardiovascular risk. Furthermore, guidelines for the management of type 2 diabetes have been updated in the US and elsewhere.^{195,196} It is unlikely, however, that a change in licence will be granted based on the current renal data, because these were not specified primary analyses in the EMPA-REG OUTCOME study and were not reported as being significant in the CANVAS analysis.

It is of note that the beneficial cardiovascular effects in both EMPA-REG and CANVAS were seen in patients with stage 3 CKD (eGFR of 30–60 mL/min/1.73 m²), for whom SGLT-2 inhibitor initiation is not currently licensed.^{165–167,171,172} This implies that the glucose-lowering efficacy of the drug class, which is lowered in CKD stage 3, is not responsible for the cardiovascular outcome reductions. It is of interest that sotagliflozin, a dual SGLT-1 and SGLT-2 inhibitor that is currently in development, also had glucose-lowering activity in a CKD stage 3 cohort with type 2 diabetes.¹⁹⁷ Thirty-one patients with an eGFR of <60 mL/min/1.73 m² were randomly assigned to receive 400 mg of sotagliflozin (LX4211) or a placebo for 7 days. LX4211 (sotagliflozin) therapy significantly reduced post-prandial glucose levels relative to the placebo in the total population and in patients with an eGFR of <45 mL/min/1.73 m². Sotagliflozin is currently being assessed as an adjunct therapy to insulin in patients with type 1 diabetes.¹⁹⁸

Studies with primary renal endpoints are already ongoing (eg CREDENCE for canagliflozin)¹⁹⁹ and these will ultimately inform whether the indication for SGLT-2 inhibitors will be broadened both within and beyond the cohort of patients who have diabetes.

9 Glucagon-like peptide-1 receptor agonists

Recommendations

- 1 There is evidence that treatment with some glucagon-like peptide-1 receptor agonists (GLP-1RAs) reduces the progression of renal disease in patients with type 2 diabetes, but this mainly relates to the new onset of persistent macroalbuminuria (Grade 2B). To date, there has been no reported reduction in hard clinical endpoints, such as a doubling of serum creatinine or the need for continuous renal replacement therapy. Hence, the main aim of GLP-1RA therapy in patients with type 2 diabetes and chronic kidney disease (CKD) should be the improvement of glycaemic control with a low risk of both hypoglycaemia and weight gain (Grade 1A).
- 2 There is emerging evidence of protection from cardiovascular disease with the use of some GLP-1RAs in patients who have type 2 diabetes and a high risk of cardiovascular disease (Grade 1A). In one sub-group analysis, this protection was more pronounced in patients with stage 3 CKD; GLP-1RAs may therefore be preferred over alternative glucose-lowering therapies (eg sulfonylureas and insulins) in this scenario (Grade 2C).
- 3 There is no evidence that any of the GLP-1RAs lead to a progressive decline in renal filtration function; however, the licensed indications differ for drugs within the class. All GLP-1RAS can be prescribed for patients with CKD stages 1–2; however, we only recommend the use of agents that have a licensed indication for CKD stages 3 and 4 (Grades 1A–1C). No GLP-1RAs are currently licensed for use in patients with CKD stage 5, or for patients who are on renal dialysis.
- 4 Patients with type 2 diabetes and CKD who are treated with GLP-1RAs need to only perform regular self-monitoring of blood glucose when they are also being treated with agents that can cause hypoglycaemia (such as sulfonylureas and insulins).
- 5 There is no role for the combination of GLP-1 analogues and dipeptidyl peptidase-4 (DPP-4) inhibitors.

Areas that require future research

- 1 There is a need for studies on GLP-1RAs that have hard renal endpoints as their primary outcome (current studies have a primary outcome of composite cardiovascular disease events, with renal outcomes being classified as secondary microvascular events).
- 2 Further studies of GLP-1RAs are needed in patients with CKD stage 5, including patients who are on renal dialysis (both haemodialysis and continuous peritoneal dialysis).
- 3 There is a need to examine the risk of worsening diabetic retinopathy in patients with type 2 diabetes and CKD treated with GLP-1RAs, in light of the fact that two studies showed deterioration despite improving proteinuria endpoints.
- 4 The use of a combination of GLP-1RAs and SGLT-2 inhibitors needs to be examined in patients with CKD, with a focus on renal endpoints.
- 5 The use of a combination of GLP-1RAs and insulin needs to be examined in patients with CKD, with a focus on renal endpoints.

Audit standards

- 1 The frequency of off-licence use of GLP-1RAs in patients with CKD stages 4 and 5.
- 2 The combination of GLP-1RA and insulin use in patients with CKD.
- 3 The combination of GLP-1RA and sodium glucose co-transporter-2 (SGLT-2) inhibitor use in patients with CKD.

Evidence base

In 2018, six licensed GLP-1RA injectables were available for use in Europe. One of these (albiglutide) has not been launched in the UK and will be withdrawn in 2018, and two involve differing delivery mechanisms for the same molecule (exenatide). All have licence limitations based on the presence of CKD, although these limitations generally become more relaxed as additional post-marketing studies are performed.

There have been isolated case reports of acute kidney injury (AKI)^{200,201} and interstitial nephritis^{202,203} resulting from exenatide and liraglutide use, and these are referred to in their summary of product characteristics (SPC).^{204,205} Acute hypovolaemia from severe gastrointestinal side effects was considered to be a more likely cause of AKI than a direct nephrotoxic effect of these agents. In practice, it would be reasonable to apply caution for patients who have CKD and acute illness via the temporary cessation of GLP-1RA therapy through general 'sick day' guidance ([Appendix B](#)).

A seventh GLP-1RA, semaglutide, has completed its phase 3 clinical trial programme and there is also a published pre-licence cardiovascular outcome trial. This agent was granted regulatory approval in the European Union (EU) in 2017.

Exenatide

Exenatide is mainly eliminated by the kidneys and its clearance is reduced by 13%, 36% and 84% in mild, moderate and severe renal disease, respectively. This leads to an increase in half-life from 1.5 hours to 2.1 hours, 3.2 hours and 6 hours in mild, moderate and end-stage renal failure (ESRF), respectively.²⁰⁶

There have been rare, spontaneously reported events of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, which sometimes require haemodialysis. Some of these occurred in patients who were experiencing events that may affect hydration (including nausea, vomiting and/or diarrhoea) and/or were receiving medicinal products that are known to affect renal function / hydration status. Concomitant medicinal products included angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor blockers (ARBs), non-steroidal anti-inflammatory drugs (NSAIDs) and diuretics. The reversibility of altered renal function has been observed with supportive treatment and discontinuation of exenatide.

In patients who are receiving exenatide as twice daily BYETTA™, no dosage adjustment is necessary if they have mild renal impairment (defined as creatinine clearance (CrCl) of 50–80 mL/min). In patients with moderate renal impairment (CrCl of 30–50 mL/min), clinical experience is very limited and dose escalation from 5 mcg to 10 mcg should 'proceed conservatively'. In patients with end-stage renal disease (ESRD) who are receiving dialysis, a single 5 mcg dose of BYETTA™ increased the frequency and severity of gastrointestinal

adverse reactions. BYETTA™ is not recommended for use in patients with ESRD or severe renal impairment (CrCl of <30 mL/min).

For once-weekly exenatide (Bydureon™), the SPC often refers to BYETTA™ data.²⁰⁷ No dose adjustment of Bydureon™ is necessary for patients with mild renal impairment (CrCl of 50–80 mL/min) but clinical experience in patients with moderate renal impairment (CrCl of 30 to 50 mL/min) is very limited, and so Bydureon™ use is not recommended for these patients. It is also not recommended for patients who have severe renal impairment (CrCl of <30 mL/min) or ESRF.

Liraglutide

Liraglutide is a once-daily GLP-1RA that is metabolised through proteolytic mechanisms and is not predominantly eliminated by a single organ.²⁰⁸ Signs and symptoms of dehydration, including renal impairment and acute renal failure, have been reported in patients who are treated with liraglutide. Patients who are treated with liraglutide should be advised about the potential risk of dehydration in relation to gastrointestinal side effects, and should take precautions to avoid fluid depletion.²⁰⁵

A single-dose (0.75 mg subcutaneously) pharmacokinetic trial with liraglutide provided initial evidence that exposure was not increased in patients with renal impairment.²⁰⁹ Thirty subjects were included in the trial: both male and female adults aged 18–85 years, with a body mass index (BMI) of <40 kg/m². CrCl was estimated using the Cockcroft–Gault formula, using the following categories:

- normal renal function (CrCl of >80 mL/min)
- mild renal impairment (CrCl of >50 to <80 mL/min)
- moderate renal impairment (CrCl of >30 to <50 mL/min)
- severe renal impairment (CrCl of <30 mL/min)
- ESRD requiring dialysis.

The ESRD group included subjects who were on continuous ambulatory peritoneal dialysis (CAPD) only and for whom CAPD was continued during the sampling period. Subjects who were receiving haemodialysis were excluded, as were renal transplant patients. There was no clear trend for change in pharmacokinetics across groups with increasing renal dysfunction. The expected area-under-the-curve (AUC) ratio between the subjects with the lowest and highest CrCl was estimated to be 0.88 (95% confidence interval (CI) 0.58–1.34), which was not significant.

Idorn²¹⁰ reported on 24 patients with type 2 diabetes and ESRD who were randomly allocated to 12 weeks of double-blind liraglutide (titrated to a maximum dose of 1.8 mg) or a placebo. Dose-corrected plasma trough liraglutide concentration was evaluated at the final trial visit as the primary outcome measure, using a linear mixed model. Twenty patients completed the study period, and dose-corrected plasma trough liraglutide concentration at the final visit was increased by 49% (95% CI 6–109; $p=0.02$) in the group with ESRD, compared with a control group of those with type 2 diabetes and normal renal function. Initial and temporary nausea and vomiting occurred more frequently among liraglutide-treated patients with ESRD, compared with the control group ($p<0.04$). The authors suggested that a reduction in treatment doses and a prolonged titration period may be advisable for patients with ESRD.

A meta-analysis from the six Liraglutide Effect and Action in Diabetes (LEAD) trials also showed that glycaemic efficacy and the safety of liraglutide in patients with mild renal impairment (estimated glomerular filtration rate (eGFR) of 60 to ≤ 89 mL/min/1.73 m²) was

similar to that in patients with normal renal function.²¹¹ Data from patients with type 2 diabetes who had normal renal function, mild renal impairment or moderate or severe renal impairment were pooled for analysis. Renal function was measured by CrCl (Cockcroft–Gault formula) in the following categories: normal renal function = CrCl of >89 mL/min; mild renal impairment = CrCl of 60–89 mL/min; and moderate or severe renal impairment = CrCl of <60 mL/min. The meta-analysis included patients who administered once-daily liraglutide (1.2 mg or 1.8 mg) or a placebo as either monotherapy or in combination with oral antidiabetic drugs for 26 weeks. In addition, a pooled analysis of all phase 2 and 3 liraglutide trials was undertaken to examine rates of altered renal function.

Mild renal impairment did not affect the estimated treatment differences in HbA1c; however, the decreases in body weight and systolic blood pressure (BP) were not significant, compared with the placebo. Liraglutide treatment versus placebo was safe and well-tolerated in patients with mild renal impairment, as there were no significant differences in rates of renal injury, minor hypoglycaemia or nausea. A trend towards increased nausea was observed in patients with moderate or severe renal impairment who were receiving liraglutide, although the number of patients in this treatment group was too low to determine significance.

The large, post-approval cardiovascular outcomes trial for liraglutide, known as LEADER, was published in June 2016.²¹² A total of 9,340 patients with type 2 diabetes were randomised, with 4,668 patients being assigned to receive liraglutide and 4,672 patients being assigned to the placebo group. In total, 96.8% of the subjects completed a final visit, died or had a primary outcome. The vital status of trial participants was known in 99.7% of cases, which indicated that it was a well-conducted study. The median time of exposure to liraglutide was 3.5 years and the mean percentage of time that patients received the trial regimen was 84% for liraglutide and 83% for the placebo. The median daily dose of liraglutide was 1.78 mg and this included periods during which subjects did not receive study medication. Overall, 2,158 (23.1%) of the LEADER patients had an estimated GFR of <60 mL/min/1.73 m², and (as mandated by the US Food and Drug Administration (FDA)) a small cohort (n=224 (2.4%)) had an eGFR of <30 mL/min/1.73 m².

The primary endpoint for the overall study (cardiovascular death, non-fatal myocardial infarction (MI) and non-fatal stroke) was reduced by 13%, showing statistical superiority for liraglutide versus the placebo. Subgroup analyses of the primary endpoint included a renal analysis that compared patients with an eGFR of <60 mL/min/1.73 m² with those above that level. Although the statistical testing was not corrected for multiple analyses, there was heterogeneity confirmed at a p value of 0.01, with patients with stage 3 CKD or worse showing greater cardiovascular disease benefit.

The LEADER trial also analysed renal events as secondary ‘microvascular’ outcomes. The renal events were as follows:

- ‘new onset of persistent macroalbuminuria’
- ‘persistent doubling of serum creatinine (and eGFR <45 mL/min)’
- ‘need for continuous renal replacement therapy’
- ‘death due to renal disease’.

Overall, there was a 22% reduction in the hazard ratio (HR) for a composite of the renal events, which was statistically significant (p=0.003). This was in contrast to the eye ‘microvascular’ event rates, which showed an elevated HR (1.14; CI 0.87–1.52), albeit non-significant. Considering the renal endpoints individually, only the new onset of persistent macroalbuminuria was significantly reduced (HR 0.74; CI 0.60–0.92), although the creatinine and renal replacement endpoints were numerically less. The number of deaths in the study that were attributable to renal disease was low (n=13). Importantly the number of other

adverse renal events (including AKI) was no different between the liraglutide and placebo groups.²¹³

The LIRA-RENAL trial was conducted to establish the efficacy and safety of liraglutide as an add-on therapy in patients with inadequately controlled type 2 diabetes and moderate renal impairment.²¹⁴ In total, 279 patients with an HbA1c of 7–10% (53–84 mmol/mol), a BMI of 20–45 kg/m², an eGFR of 30–59 mL/min/1.73 m² and modification of diet in renal disease (MDRD) were randomised to 1.8 mg liraglutide once daily or a placebo. The treatment difference in HbA1c from the baseline to week 26 was 0.66%, and there was a greater reduction in body weight with liraglutide (–2.41 kg) than with the placebo (–1.09 kg). No changes in renal function were observed: the most common adverse events were gastrointestinal side-effects and there was no difference in hypoglycaemia between the treatment groups.

As a result of this study evidence, no dose adjustment of liraglutide is required for patients with mild or moderate renal impairment (CrCl of 60–90 mL/min and 30–59 mL/min, respectively).

At the request of the FDA, the LEADER study included 224 patients with severe renal impairment (eGFR <30 mL/min/1.73 m²), of whom 117 were randomised to receive liraglutide.^{212,213} As a result of this, the SPC for the EU was updated on 25 July 2017 to state the following: ‘No dose adjustment is required for patients with mild, moderate or severe renal impairment’ ie liraglutide can be used in patients with an eGFR of >15 mL/min. There is little therapeutic experience in patients with ESRD, so liraglutide is currently not recommended for use in this cohort.

The Association of British Clinical Diabetologists’ (ABCD’s) nationwide audit of real-world liraglutide use in patients with mild and moderate renal impairment confirmed that a 1.2 mg dose was safe and efficacious with respect to both glycaemic control and weight, although discontinuation due to gastrointestinal side effects was greater among those with renal impairment than those without.²¹⁵

Lixisenatide

Lixisenatide is a once daily GLP-1RA that has a shorter half-life than liraglutide. It is usually classed as a short-acting GLP-1RA that has a predominant action on post-prandial glucose excursions, possibly mediated by slowed gastric emptying.

No dose adjustment is required for patients with mild renal impairment (defined as CrCl of 50–80 mL/min) but monitoring for changes in renal function is recommended because a higher incidence of hypoglycaemia, nausea and vomiting was observed in these patients during clinical trials.²¹⁶ There is limited therapeutic experience in patients with moderate renal impairment (CrCl of 30–50 mL/min), so it is recommended that lixisenatide should be used ‘with caution’ in this population, with close monitoring for adverse gastrointestinal adverse effects and renal changes. An ongoing study (Effect of LIXIsenatide on the Renal System (ELIXIRS)) is currently examining the impact of lixisenatide on renal function in 40 patients with type 2 diabetes.²¹⁷

There is no therapeutic experience of lixisenatide use in patients with severe renal impairment (CrCl of <30 mL/min), where only five such patients were included in the controlled studies. Similarly, there is no experience in those with ESRF (CrCl of <15 mL/min) and, therefore, lixisenatide use is not recommended in these patients.

Dulaglutide

Dulaglutide is a once weekly GLP-1RA that is available in 0.75 mg and 1.5 mg doses via a disposable injection device.²¹⁸ It is presumed to be degraded into its component amino acids by general protein catabolism pathways. The pharmacokinetics of dulaglutide were evaluated in a clinical pharmacology study and were generally similar between healthy subjects and patients with mild to severe renal impairment (CrCl of <30 mL/min), including those with ESRF (requiring dialysis).²¹⁹ In clinical studies, the dulaglutide safety profile in patients with moderate renal impairment was similar to the profile in the overall type 2 diabetes population. These studies did not include patients with severe renal impairment or ESRD. A 26-week study comparing dulaglutide with insulin glargine in participants with type 2 diabetes and moderate or severe CKD (AWARD-7) has reported comparable glycaemic control.²²⁰ Dulaglutide, however, led to greater weight loss and less hypoglycaemia than insulin glargine. In addition, eGFR decline was mitigated and albuminuria was reduced: these benefits were most evident when the albumin:creatinine ratio (ACR) exceeded 30 mg/g.²²¹

As a result of these data, no dosage adjustment is required in patients with mild, moderate or severe renal impairment (eGFR of <90 to ≥ 15 mL/min/1.73 m²).²²² Given that there is very limited experience in patients with an eGFR of <15 mL/min/1.73 m² or ESRF, dulaglutide use is not recommended in these patients.

Albiglutide

Albiglutide is a recombinant fusion protein that is composed of two copies of a 30-amino acid sequence of modified human GLP-1 genetically fused in series to human albumin. The recommended starting dose of albiglutide is 30 mg once weekly, administered subcutaneously; this may be increased to 50 mg once weekly, based on the individual glycaemic response.²²³

In a population pharmacokinetic analysis that included a phase III trial in patients with mild, moderate and severe renal impairment, exposures were increased by approximately 30% to 40% in severe renal impairment, compared with patients with type 2 diabetes and normal renal function. In addition, a clinical pharmacology study showed a similar increased exposure for patients with moderate or severe renal impairment or those on haemodialysis, relative to patients with no renal impairment. These differences were not considered to be clinically relevant.²²⁴

The efficacy of albiglutide was evaluated in a randomised, double-blind, active-controlled 52-week study in 486 patients with mild, moderate and severe renal impairment that was inadequately controlled on a current regimen of diet and exercise or other antidiabetic therapy.²²⁵ Albiglutide 30 mg subcutaneously weekly (with up-titration to 50 mg weekly if needed) was compared with sitagliptin, and the primary endpoint was a change in HbA1c from the baseline at 26 weeks. Treatment with albiglutide resulted in statistically significant reductions in HbA1c from the baseline at week 26 compared with sitagliptin. The model-adjusted mean decrease in HbA1c from the baseline with albiglutide was -0.80 (n=125), -0.83 (n=98) and -1.08 (n=19) in patients with mild (eGFR of 60–89 mL/min/1.73 m²), moderate (eGFR of 30–59 mL/min/1.73 m²) and severe (eGFR of <30 mL/min/1.73 m²) renal impairment, respectively.

On the basis of these data, no dose adjustment is necessary for patients with mild and moderate renal impairment (eGFR of 60–89 and 30–59 mL/min/1.73 m², respectively). Experience in patients with severe renal impairment (eGFR of <30 mL/min/1.73 m²) or those

on dialysis is very limited, but there was a higher frequency of diarrhoea, nausea and vomiting. For these reasons, albiglutide is not recommended in this cohort.

On 26 July 2017, GSK announced that albiglutide will be withdrawn from all markets by July 2018 and it advised that no new patients should be initiated on this agent.²²⁶

Semaglutide

Semaglutide is a GLP-1RA with an extended half-life of approximately 1 week, permitting once-weekly subcutaneous dosing. It was given market authorisation for the treatment of type 2 diabetes in Europe in February 2018. The SUSTAIN 6 trial²²⁷ was initiated pre-approval and designed to assess non-inferiority of semaglutide compared with a placebo, in terms of cardiovascular safety in patients with type 2 diabetes. Overall, 3,297 patients underwent randomisation, of whom 3,237 (98.0%) attended the last follow-up visit (at an investigator site or by a phone visit) or died during the trial. Vital status was known for 99.6% of the patients at the end of the trial. The median observation time was 2.1 years. The mean percentage of time on the trial medication was 86.5% for semaglutide and 89.5% for the placebo.

The composite primary outcome (cardiovascular death, non-fatal MI and non-fatal stroke) occurred in significantly fewer semaglutide-treated patients (108 out of 1,648 (6.6%)) compared with the placebo-treated patients (146 out of 1,649 (8.9%)) (HR 0.74; CI 0.58–0.95; $p=0.02$ for superiority, a non-specified statistical analysis). Recruits were included in the trial down to an eGFR of 31 mL/min/1.73 m², but subgroup analyses according to eGFR have not yet been published.

As was the case in the LEADER trial, renal microvascular outcomes were pre-specified secondary outcomes, and there was a significant reduction of the composite renal endpoints (HR 0.64; CI 0.46–0.88; $p=0.005$). This benefit was driven by a fall in new cases of persistent macroalbuminuria (2.5% versus 4.9% of cases) whereas the number of patients who had a doubling of serum creatinine and/or needed continuous renal replacement therapy was small and similar between groups.

Diabetic retinopathy endpoints were experienced by significantly more patients who were treated with semaglutide (50 patients (3.0%)) than the placebo (29 patients (1.8%)). The reason for this is unknown, but a high baseline prevalence of significant retinopathy, a higher baseline HbA1 than in other studies and a rapid marked decline in blood glucose levels may together have contributed to this outcome.²²⁸ Further analyses and studies are awaited.

According to the summary of product characteristics (SPC), no dose adjustment of semaglutide is required for patients with mild, moderate or severe renal impairment and so it may be used in patients with an eGFR of >15 mL/min/1.73 m². Experience with the use of semaglutide in patients with severe renal impairment is limited. Semaglutide is not recommended for use in patients with ESRF.²²⁹

Declarations of interest

The authors declare the following potential conflicts of interests and support from industry.

- Stephen Bain has received honoraria, teaching and research sponsorship/grants from: Abbott, AstraZeneca, Boehringer Ingelheim, BMS, Cellnovo, Diartis, Eli Lilly, GSK, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi Aventis, Schering-Plough and Servier & Takeda. He has also received funding for the development of educational programmes from: Cardiff University, Doctors.net, Elsevier, OnMedica, OmniaMed and Medscape. He is a partner in Glycosmedia, which carries sponsorship declared on its website.
- Debasish Banerjee was previously funded for research by the British Heart Foundation (BHF).
- Indranil Dasgupta has previously received research grants from Medtronic and Daiichi Sankyo. He has been a member of advisory committees and received educational grants from AstraZeneca, Amgen, Sanofi, MSD, Pfizer, GSK, Mitsubishi Pharma, Otsuka, Vifor Pharmaceuticals, Fresenius and Roche.
- Parijat De has received honoraria for educational meetings from Astra Zeneca, Janssen, Boehringer Ingelheim, Novo, Sanofi, Novartis, Abbott, MSD, Takeda, Roche, Lilly, Ascensia, BD, Internis, GSK, Menarini, Bayer and Besins.
- Damian Fogarty has received honoraria for delivering educational meetings and/or attending advisory boards from AstraZeneca, Sanofi, Vifor Pharmaceuticals and Baxter. He provides consultancy for adjudication of endpoint in RCTs to ACI.
- Andrew Frankel has received research grants, and he prepares educational materials and attends drug advisory boards for: Boehringer Ingelheim/Lilly Alliance, AstraZeneca, Novo Nordisk, Merck and Johnson & Johnson.
- Ana Pokrajac has received honoraria for attending and delivering non-promotional educational meetings and advisory boards from Lilly, NovoNordisk and Boehringer Ingelheim.
- Peter Winocour has received honoraria for delivering educational meetings and/or attending advisory boards for AstraZeneca, Eli Lilly, Novo Nordisk, Sanofi, MSD, Janssen and Vifor Pharmaceuticals.

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Appendix A – Antihyperglycaemics in CKD

		Renal impairment – CKD stage						
Drug	Class of drug	1 (eGFR >90)	2 (eGFR 60–90)	3a (45–59)	(eGFR)	3b (eGFR 44–30)	4 (eGFR 29–15)	5 (eGFR <15)
Metformin	Biguanide					Reduce dose to 500 BD*	eGFR may underestimate in obesity; potential role for 500 mg	
Gliclazide	Sulphonylurea	CBG	CBG	CBG		Dose reduction advised CBG	Off licence, high risk of hypoglycaemia CBG	
Repaglinide	Meglitinide	CBG	CBG	CBG		CBG	Dose reduction advised CBG	Dose reduction advised CBG
Sitagliptin	DPP-4i			<50 mL/min reduce dose to 50 mg		Reduce dose to 50 mg	Reduce dose to 25 mg	Reduce dose to 25 mg
Saxagliptin	DPP-4i			<50 mL/min reduce dose to 2.5 mg		Reduce dose to 2.5 mg	Reduce dose to 2.5 mg	
Linagliptin	DPP-4i							
Pioglitazone**	Thiazolidinedione							
Lixisenatide	GLP-1 agonist			Caution in CrCl§ <50 mL/min				
Exenatide	GLP-1 agonist			Caution in CrCl*** <50 mL/min		Conservative dosing		
Exenatide MR	GLP-1 agonist			Stop if CrCl§ <50 mL/min				
Liraglutide	GLP-1 agonist						Dose reduction might be needed	Off licence, few small studies suggest no harm****
Dulaglutide (Trulicity)	GLP-1 agonist							
Dapagliflozin	SGLT-2i			Reduce dose to 5 mg				
Canagliflozin	SGLT-2i			Reduce dose to 100 mg				
Empagliflozin	SGLT-2i			Reduce dose to 10 mg				
Insulin						Dose reduction may be needed	Dose reduction should be needed	

* Sick day guidance

** Monitor for fluid retention, contraindicated in heart failure, macular oedema

*** CrCl – creatinine clearance as an estimate of glomerular filtration rate (GFR), usually calculated using Cockcroft–Gault equation

**** Use of Liraglutide for eGFR <15 mL/min is off licence as there is insufficient evidence of substantial grade, but some studies suggest no harm, which is in keeping with its liver metabolism

Appendix B – Medicines sick day guidance

Medicines sick day guidance

Omit taking the medications listed below when you are unwell with any of the following:

- *persistent* vomiting or diarrhoea
- fever *with* significant sweating and shaking.

These medications are all very important, but when you are seriously ill or become dehydrated, they *may* cause side effects.

These medications can be restarted once you start eating and drinking normally *after* 24–48 hours. If your sickness lasts longer than that, *you would be best advised to seek medical attention.*

If you have diabetes and you usually monitor your blood glucose at home, increase the number of times that you check your blood glucose levels. If your levels run too high or too low, contact your diabetes team.

If you are taking insulin, seek medical advice regarding dose adjustment if you are uncertain, but never stop taking the insulin.

If you are in any doubt, contact your pharmacist, GP or nurse.

Medications to omit temporarily

Metformin

SGLT-2 inhibitors: medicine names ending in ‘flozin’
eg canagliflozin, dapagliflozin and empagliflozin

SGLT-2: medicine names ending in ‘tide’
eg exenatide, liraglutide, dulaglutide and lixisenatide

ACE inhibitors: medicine names ending in ‘pril’
eg lisinopril, perindopril and ramipril

ARBs: medicine names ending in ‘artan’
eg losartan, candesartan and valsartan

NSAIDs: anti-inflammatory painkillers
eg ibuprofen, diclofenac and naproxen

Diuretics: sometimes called ‘water pills’
eg furosemide, indapamide, bendroflumethiazide, bumetanide and spironolactone

ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; NSAIDs = non-steroidal anti-inflammatory drugs; SGLT = sodium-glucose cotransporter.