



Clinical practice guidelines for management of hyperglycaemia in adults with diabetic kidney disease

2021 update

Endorsed by:



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of Physicians**

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1 Introduction

A significant percentage of people with diabetes develop chronic kidney disease (CKD), and diabetes is also a leading cause of end-stage kidney disease (ESKD).¹ More than a quarter of people who are on dialysis in the UK have diabetes.² Diabetic kidney disease (DKD) is associated with high morbidity and mortality, which are predominantly related to cardiovascular complications and the progression to kidney disease that requires renal replacement therapy. Hyperglycaemia is a modifiable risk factor for cardiovascular complications and progression of CKD.³ In addition to standard blood glucose assessment and management and appropriate treatment for hyperglycaemia and avoidance of hypoglycaemia, drugs such as SGLT-2 inhibitors and GLP-1 analogues have demonstrated improvement in clinical outcomes independent of glucose lowering and in the future may be used primarily in the prevention and treatment of DKD.

This guidance is for the variety of clinicians who treat people with diabetic kidney disease, including GPs and specialists in diabetes, cardiology and nephrology. It intends to harmonise practices of blood glucose monitoring, and pharmacological and non-pharmacological management of hyperglycaemia, which may vary considerably.

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 review of the Cochrane Library, PubMed/MEDLINE, Google Scholar and Embase carried out initially between October 2013 and December 2016 and further review carried out in December 2020 for the current update, using the following keywords: type 1 diabetes, insulin, chronic kidney disease, nephropathy, hyperglycaemia, hypoglycaemia, insulin, sulfonylureas, metformin, SGLT-2 inhibitors, pioglitazone, DPP-4 inhibitors, GLP-1 analogues and meglitinides.

Note on revisions

This guidance updates *Managing hyperglycaemia in patients with diabetes and diabetic nephropathy-chronic kidney disease* published in May 2018. For ease of recognition, key revisions and additions have been highlighted in pale yellow like this.

Classification

The guidance uses following descriptions to differentiate and classify kidney disease. Diabetic kidney disease (DKD) is used throughout as a suitable umbrella term to include both diabetic nephropathy (DN) and diabetes mellitus and chronic kidney disease (DM CKD).

Table 1 Differentiating kidney disease in diabetes

Diabetic nephropathy	Damage to the glomerular capillaries in people with diabetes mellitus resulting in albuminuria in the absence of other causes of albuminuria.
Diabetes mellitus and chronic kidney disease	The presence for more than 3 months of structural renal abnormalities with reduced glomerular filtration in people with diabetes mellitus.

Fig 1 Renal Association classification of estimated glomerular filtration rates (eGFRs) and albumin:creatinine ratio (ACR) categories

GFR and ACR categories and risk of adverse outcomes			ACR categories (mg/mmol), description and range		
			<3 Normal to mildly increased	3–30 Moderately increased	>30 Severely increased
			A1	A2	A3
GFR categories (ml/min/1.73m ²), description and range	≥90 Normal and high	G1	No CKD in the absence of markers of kidney damage		
	60–89 Mild reduction related to normal range for a young adult	G2			
	45–59 Mild–moderate reduction	G3a ¹			
	30–44 Moderate–severe reduction	G3b			
	15–29 Severe reduction	G4			
	<15 Kidney failure	G5			

Increasing risk ↓

→ Increasing risk

¹ Consider using eGFR_{cystatinC} for people with CKD G3aA1 (see recommendations 1.1.14 and 1.1.15)

Abbreviations: ACR, albumin:creatinine ratio; CKD, chronic kidney disease; GFR, glomerular filtration rate

Adapted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International (Suppl. 3): 1–150

2 Glycaemic targets in the prevention and management of diabetes and chronic kidney disease

Recommendations

- 1 Individualised HbA1c targets should be applied in the management of people with diabetes and DKD, using the levels suggested in [Table 2](#) (Grade 1B).
- 2 It is important to ensure that anaemia has been excluded or considered when using HbA1c to assess glycaemia (Grade 1B).
- 3 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 (Grade 1B).
- 4 The selection of individual classes of medication, tailored to the additional comorbidities that are frequently seen alongside DKD, will also influence therapy selection ([Table 3](#)) (Grade 1B).
- 5 Certain combinations of different classes of drugs need judicious consideration, but appropriate combinations of different classes will frequently be used to manage diabetes in people with CKD ([Table 4](#)) (Grade 1B).

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 with 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 diabetes with or without CKD,^{4,5} and consensus groups have extrapolated from contemporary general recommendations, such as with Kidney Disease Outcomes Quality Initiative (KDOQI) in 2012,⁶ which suggested a target HbA1c level of 53 mmol/mol (7%) in those with CKD stage 5 and the more recent clinical practice guideline on older, frail people with DKD provided by ERA-EDTA.⁷

By contrast, the European Renal Best Practice (ERBP) guidance in 2015 recognised the lack of prospective randomised trials in CKD stage 3b or higher, 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.⁸

A retrospective observational case cohort study found that HbA1c levels of 48 mmol/mol (<6.5%) and 63 mmol/mol (>8%) were associated with increased mortality in people with CKD stages 3–4.⁹

The most recent Cochrane collaborative meta-analysis from 2017 found that there were comparable risks of end-stage kidney disease (ESKD), death and major cardiovascular events

among people with stringent glycaemic control (HbA1c 54 mmol/mol (<7%)), as opposed to those with less tight control, beyond small clinical benefits on the onset and progression of microalbuminuria.¹⁰

There has been an important shift in emphasis in recent guidance from the American Diabetes Association, the European Association for the Study of Diabetes, and the European Society for Cardiology. There is now specific emphasis on selection of sodium glucose cotransporter 2 inhibitors or glucagon like peptide 1 receptor agonists where, in addition to glucose lowering, these therapies should be considered in people with chronic kidney disease where there is an evidence base for cardiorenal protection.^{11–13}

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 43 mmol/mol (6%) (achieved 55 mmol/mol (7.2%)). The study clearly demonstrated a reduced incidence for the development and progression of microalbuminuria and macroalbuminuria in the primary and secondary prevention groups.¹⁴ Furthermore, ongoing surveillance for up to 18 years with less intensive glycaemic control (HbA1c subsequently maintained at a mean of 63 mmol/mol (8%)) 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.¹⁵

At trial entry, none of the participants 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.¹⁴

A 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 (6.9%). 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.¹⁶

All-cause and cardiovascular mortality, however, in those with renal disease was virtually unchanged for people with a time-updated HbA1c of 53–62 mmol/mol (7.0–7.8%) versus those with values of 52 mmol/mol (6.9%) or lower, which suggests that there is no additional benefit of tighter glycaemic control in those with type 1 diabetes who have renal disease.¹⁶ Thus it would be appropriate to reduce the development and progression of nephropathy via tight glycaemic control in younger people (HbA1c target individualised to 48–58 mmol/mol (6.5–7.5%)), with a requirement to at least maintain moderate control (HbA1c of <63 mmol/mol (7.9%)) after a period of 10 years. There are, however, vascular benefits from tight glycaemic control (target HbA1c of 48–58 mmol/mol (6.5–7.5%)) over a longer period in younger people 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 (6.5%) utilises the DCCT target¹⁷ which, although rarely achieved in that study, reduced both the progression of microalbuminuria to overt albuminuria (macroalbuminuria) and development of microalbuminuria. From intervention studies with people with type 1 diabetes who have DKD with albuminuria, there is no current evidence that renal or other outcomes are improved by achieving an HbA1c of 48 mmol/mol (6.5%).

While recognising that individualised care targets should apply, it may still be broadly reasonable to aim for an HbA1c of 58–62 mmol/mol (7.5–7.8%) in people with type 1 diabetes who have DKD up to CKD stages 3–4, unless values of 48–58 mmol/mol (6.5–7.5%) are achievable in younger people (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. Access to continuous blood or flash glucose monitoring will increasingly enable the HbA1c targets to be met while reducing hypoglycaemic frequency.

The Joint British Diabetes Societies (JBDS) guidelines for people with diabetes of any type who are on haemodialysis recommended HbA1c targets of 58–68 mmol/mol (7.5–8.4%). 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,¹⁸ which is present in 18–27% of people with CKD stage 3 and is even more prevalent in those with more advanced CKD.^{19,20} Renal anaemia occurs in people with diabetes with earlier stages of CKD compared with those without diabetes.²¹ Renal anaemia can affect the accuracy of HbA1c, with normochromic secondary anaemia leading to falsely lower HbA1c²² while iron deficiency artefactually elevates the HbA1c value, and should be interpreted with these caveats in mind.²³

Type 2 diabetes

With the exception of younger people who have type 2 diabetes (below the age of 40) where the lifetime renal–cardiovascular disease risk may justify similar glycaemic targets to those 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 160 participants 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 (6.5%), the mean HbA1c that was achieved in the study with an insulin-dominant regime was 63 mmol/mol (7.9%). 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.^{24,25}

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. In the longer term follow up study the decline in measured GFR (by 51-Cr-EDTA) was significantly different with 3.1 ml/min/year in the intensive-therapy group compared to 4.0 in the conventional-therapy group.²⁶ Although the sample size was small, there was also a borderline significant reduction in progression to ESKD ($p=0.06$).

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/mol and 59 mmol/mol (7.5%) in the intensive and control groups at 21 years' follow-up.²⁵

By contrast, the ACCORD study design (with a target HbA1c of 42 mmol/mol (6.0%) 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.²⁷

In people who did not have CKD at trial entry, there was a delay in the onset of albuminuria but no reduction in their progress towards ESKD or the need for renal replacement therapy, and this was achieved at the cost of a high risk for severe hypoglycaemia and increased mortality.²⁸

The ADVANCE study was a predominantly sulfonylurea-based study and it recorded that intensive glucose control to a target HbA1c of 48 mmol/mol (6.5%) reduced the development and progression of both albuminuric and glomerular filtration outcomes in people with type 2 diabetes, although the number of events was low.²⁹ Over 5 years, the numbers needed to treat (NNT) to prevent one end-stage kidney event ranged from 410 participants in the overall study to 41 participants with macroalbuminuria at baseline.^{29,30}

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.^{30,31}

Two recent meta-analyses demonstrated that, although intensive glucose control (target HbA1c 43–54 mmol/mol (6.1–7.1%)) can lead to a reduced incidence of the surrogate renal measures of microalbuminuria and macroalbuminuria in people with type 2 diabetes, there was no significant impact on clinical renal outcomes such as a doubling of serum creatinine, progression to ESKD, death from kidney disease or other complications.^{32,33} A more recent meta-analysis included data from the Veteran Affairs (VA) and UK Prospective Diabetes Study (UKPDS) studies implied that intensive glycaemic control had benefits in reducing these hard renal outcomes, but the heterogeneity of glycaemic targets limits the validity of that conclusion.³⁴

The most recent review of the Veterans Affairs Diabetes Trial (VADT) used a composite endpoint of sustained estimated glomerular filtration rate (eGFR) <45 mL/min/1.73m² or urine albumin-to-creatinine ratio >33.9 mg/mmol (>300 mg/g). The median HbA1c achieved was 15 mmol/mol (1.5%) lower in intensive vs. standard treatment during the intervention phase (52 vs. 68 mmol/mol (6.9% vs. 8.4%)). At the end of the interventional period, there was a nonsignificant 13% reduction in time to occurrence of the composite renal outcome in the intensive treated group (95% CI 0.70–1.074; p=0.19). However, at the 10-year interim analysis, the composite renal outcome was 22.7% in intensive and 27.0% in line with standard treatment, with a 20% reduction in the time to composite renal outcome in the intensive group (95% CI 0.66–0.96; p=0.02). By the end of the final VADT follow-up in 2017, composite outcome was reached by 25.7% with intensive treatment and 29.7% with standard treatment, a 19% reduction through intensive treatment (95% CI 0.68–0.97; p=0.02). In this extended follow-up of the VADT cohort for 15 years, 5.6 years of intensive glucose lowering reduced a composite renal outcome of development of persistent stage 3b chronic kidney disease or ACR >33.9 mg/mmol (>300 mg/g). Consistent with other trials, there was a lag time for the effects of intensive glucose control to manifest. Of interest is that the beneficial renal effect was sustained even after the separation of 15 mmol/mol (1.5%) in HbA1c had disappeared. This is in keeping with the stated legacy effect of glycaemic control and recognition that the benefit may be delayed. However, it should be recognised that in this relatively small trial the dominant driver of outcome was progression of albuminuria rather than a hard renal outcome such as doubling of serum creatinine or onset of ESKD.³⁵

Given these discrepancies, the Cochrane collaboration initiated a review in 2015 to examine the efficacy and safety of insulin and other pharmacological interventions for lowering blood glucose in people with diabetes and CKD. This was published in 2018. It concluded that evidence concerning the efficacy and safety of glucose-lowering drugs for people with DKD is

limited, SGLT-2 inhibitors and GLP-1 agonists are probably efficacious for lowering glucose levels. Other potential effects of SGLT-2 inhibitors included lower blood pressure, lower potassium levels and a reduced risk of heart failure but an increased risk of genital infections. The safety of GLP-1 agonists was stated to be uncertain and the benefits and safety of other classes of glucose-lowering agents are uncertain. They concluded that more studies were required to help guide clinicians on which glucose-lowering medications were most suitable in people with DKD.³⁶

The JBDS has already reported and suggested an HbA1c of 58–68 mmol/mol (7.5–8.4%) in people 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.¹⁸

On balance, whereas the lifelong risk that hyperglycaemia will lead to the development and progression of DKD (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 53 mmol/mol (<7%).

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

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 (A2) and 11% had macroalbuminuria (A3).³⁷ The cohort with a reduced eGFR had a baseline HbA1c of 65 mmol/mol (8.1%), which fell to 60 mmol/mol (7.6%) – only 3 mmol/mol (0.3%) 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.³⁷ A more recent evaluation of albuminuria progression confirmed these findings.³⁸

In the only study to date solely in people with established DKD (with or without CVD) (CREDENCE),³⁹ similar cardiorenal benefits to those in EMPA-REG were evident with attained reductions in HbA1c to 61–65 mmol/mol (7.7–8.1%).

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 72 mmol/mol (8.7%) at entry was set against a target HbA1c of 53 mmol/mol (7%), and the achieved HbA1c with liraglutide of 60 mmol/mol (7.6%) was only 4 mmol/mol (0.4%) 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.⁴⁰

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 72 mmol/mol (8.7%), the active treatment led to a reduction in HbA1c to 56–60 mmol/mol (7.3–7.6%) depending on the dosage, which was 7–10 mmol/mol (0.7–1%) lower than the control group. New or worsening nephropathy was reduced by 36% with active treatment, essentially through a reduction in progression to macroalbuminuria.⁴¹ The most recent study to evaluate renal function with dulaglutide (the REWIND study) achieved reduction in progression to macroalbuminuria with a reduction in HbA1c of 6 mmol/mol (0.61%) compared with placebo, from a baseline of 56 mmol/mol (7.3%).⁴²

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 focus in more detail on these studies and the available glucose-lowering therapies for people who have diabetes and DKD.

At present, it would be prudent to consider an HbA1c target of 58 mmol/mol (7.5%) for most people with type 2 diabetes and DKD if they are on an insulin-dominant regime, and a target of up to 68 mmol/mol (8.4%) in older people with more advanced CKD (stage 4 or higher).

It remains to be seen whether it is appropriate and safe to have a lower glycaemic HbA1c target of 52 mmol/mol (6.9%) in people 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 for people with and without cardiovascular disease.

From the current evidence, there is no basis to seek HbA1c values of lower than 52 mmol/mol (6.9%) in older people with type 2 diabetes and DKD through medication. Those managed solely with dietary therapy will often attain lower HbA1c values without hypoglycaemia, not least if renal anaemia has led to artefactually lower values. Complementary direct glycaemia measurement and/or flash subcutaneous glucose measures can be utilised to better gauge the potential for hypoglycaemia especially when HbA1c may be misleading. To date there is limited data on flash glucose sensing in ESKD. Trials are ongoing to assess the effectiveness of the FreeStyle Libre system compared with continuous glucose monitoring (CGM).

Conclusion

Individualised HbA1c targets should be applied in the management of people with DKD, using the levels suggested in [Table 2](#). 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 drug, tailored to the additional comorbidities that are frequently seen alongside DKD, will also influence therapy selection ([Table 3](#)). In addition, certain combinations of different classes of drugs would need judicious consideration ([Table 4](#)). Although these current guidelines focus on the individual classes of glucose-lowering drug, combinations of different classes will frequently be used to manage diabetes in people with CKD. There is a relative dearth of studies that specifically evaluate different drug combinations in people with DKD, and this is clearly an area for both further research and current clinical audit ([Table 5](#)).

Table 2 Glycaemic targets in people with DKD

Condition	Glycaemic target	CKD stage and albuminuria	Age
Type 1 diabetes	48–58 mmol/mol (6.5–7.5%)*	CKD stage 2 with variable microalbuminuria	Younger people within 10 years' duration of diabetes
	58–62 mmol/mol (7.5–7.8%)	CKD stages 3–4 and/or albuminuria	The majority of people
	58–68 mmol/mol (7.5–8.5%)	CKD stage 5 – dialysis	Any age
Type 2 diabetes	48–58 mmol/mol (6.5–7.5%)* Aim for <52 mmol/mol (6.9%)	CKD stages 1–2	People who are aged <40 **Diet controlled at any age
	52–58 mmol/mol (6.9–7.5%)	CKD stages 3–4 May be appropriate with a GLP-1 and/ or SGLT-2 inhibitor-based treatment regime without insulin	Any age
	58–68 mmol/mol (7.5–8.5 %)	CKD stages 3–4 and those with CKD stage 5 who are on dialysis. Especially in people with albuminuria who are on an insulin-based regime ▽	Any age

*Confirmatory blood glucose or flash glucose monitoring if concern of hypoglycaemia and/or anaemia

▽ Recognition of cardiorenal benefits with SGLT-2 inhibitors (and potentially GLP-1 analogue therapy) independent of glycaemic effect

**Over 20% of people with DKD (especially older people aged >75) solely dietary controlled can have HbA1c 42–48 mmol/mol (6–6.5%) without hypoglycaemia

Table 3 Contraindications to the selection of blood glucose-lowering therapies in people with DKD with DM complications

Condition	Drug	Note
Retinopathy	Pioglitazone	Absolute contraindication in diabetic maculopathy
	Semaglutide	Relative contraindication in people with marked hyperglycaemia (HbA1c >91 mmol/mol (10.5%)) who have diabetic retinopathy requiring active ophthalmology follow-up: caution is advised
Bone health	Pioglitazone	Absolute contraindication in people who have had previous osteoporotic fractures; or relative contraindication in those with post-menopausal osteoporosis with neuropathy
	SGLT-2 inhibitors	Relative contraindication in people with established osteoporotic fractures.
Foot health	SGLT-2 inhibitors	Absolute contraindication if a person has active diabetic foot disease with vascular complications or sepsis.
Cardiac failure	Pioglitazone	Absolute contraindication in people with established treated

Condition	Drug	Note
		heart failure and where at-risk people have a raised serum brain natriuretic peptide (BNP)
	Saxagliptin	Absolute contraindication in people with treated established heart failure
Pancreatic health	GLP-1 analogues	Absolute contraindication of GLP-1 analogues where an individual has previously documented pancreatitis; relative contraindication in people who are at risk of pancreatitis with raised triglycerides, those on steroid therapy, those using other drugs that are associated with pancreatitis or those with documented alcoholism
Bladder health	SGLT-2 inhibitors	Relative contraindication of all medications in this class in people who have documented neuropathic bladder and recurrent urinary infections
	Pioglitazone	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	GLP-1 analogues	Relative contraindication if a person has active gall bladder disease ^{43,44}

Table 4 Cautions when using combinations of drug classes to treat diabetes in people who have CKD*

1	Insulin and sulfonylurea combination in people with more advanced CKD (stages 4–5)
2	SGLT-2 inhibitors and pioglitazone combination in people with evident metabolic bone disease
3	Insulin and pioglitazone combination in people 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

*These cautions are in addition to the current guidance for prescribing in renal impairment according to the lowest eGFR for a given drug.

Traditionally, the licensing of medicinal products in relation to renal dysfunction utilised creatinine clearance (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 can be used or to adjust medication dosages in diabetes.⁴⁵ The British National Formulary (BNF) provides a useful summary.⁴⁶

It is important to recognise that eGFR equations that are currently in use underestimate kidney function in people who are obese (BMI >30 kg/m²) with type 2 diabetes.⁴⁷ 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 the kidney function is monitored appropriately to ensure that the treatment is stopped when the renal function moves out of the licensing range.

Table 5 Action to be taken when treating people with DKD by medication

Pioglitazone	
eGFR level	Action to be taken
For all	<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 people who develop osteoporotic fractures.
>60 mL/min/1.73 m²	<ul style="list-style-type: none"> No renal contraindication to pioglitazone.
45–60 mL/min/1.73 m²	<ul style="list-style-type: none"> Continue use in people who are established on pioglitazone but monitor for fluid retention every 3–6 months. For new individuals 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 weeks.
30–45 mL/min/1.73 m²	<ul style="list-style-type: none"> In people who are established on pioglitazone, monitor for fluid retention every 3–6 months. People can be started at 15 mg once daily and titrated up, based on the effectiveness and development of fluid retention in 2 weeks.
<30 mL/min/1.73 m²	<ul style="list-style-type: none"> In those who are established on pioglitazone, monitor for fluid retention every 3 months. People can be started at 15 mg once daily and titrated up, based on the effectiveness and development of fluid retention in 2 weeks.
Dialysis	<ul style="list-style-type: none"> People can be started at 15 mg once daily and titrated up, based on the effectiveness and development of fluid retention in 2 weeks (note the risk of fluid retention is offset by dialysis). In those who are established on pioglitazone, monitor for fluid retention every 3 months.

Nateglinide and repaglinide	
eGFR level	Action to be taken
For all	<ul style="list-style-type: none"> Practitioners have to weigh up the risk of hypoglycaemia. To be taken prandially
>60 mL/min/1.73 m²	<ul style="list-style-type: none"> Continue or commence nateglinide or repaglinide. Advise people to monitor their capillary blood glucose (CBG) 2 hours after taking the medication and to take precautions when driving.
45–60 mL/min/1.73 m²	<ul style="list-style-type: none"> Continue or commence nateglinide or repaglinide. Advise people to monitor their CBG 2 hours after taking the medication and to take precautions when driving.
30–45 mL/min/1.73 m²	<ul style="list-style-type: none"> Continue or commence nateglinide or repaglinide. Advise people to monitor their CBG 2 hours after taking the medication and to take precautions when driving.
<30 mL/min/1.73 m²	<ul style="list-style-type: none"> Review the dose of nateglinide or repaglinide if the person is already taking it, and consider a reduction based on their CBG. Advise people to monitor their CBG 2 hours after taking medication and to take precautions when driving. Commence nateglinide or repaglinide at half the regular dose.
Dialysis	<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 people to take precautions when driving. Increased monitoring is required while someone is on these medications. Advise people to take with meals.

Metformin	
eGFR level	Action to be taken
For all	<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 the information leaflet <i>Advice for patients taking metformin</i>.
>60 mL/min/1.73 m²	<ul style="list-style-type: none"> No renal contraindication to metformin. Some of these people 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 m²	<ul style="list-style-type: none"> Continue use in people who were established on metformin, but review the dose in light of glucose control needs. For new individuals 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 m²	<ul style="list-style-type: none"> Continue or commence with caution and explain the risks and benefits to the person. Use 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 m²	<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 metformin in selected people 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 people who are obese. The Cockcroft–Gault formula may give a better reflection of eGFR in obese people, and may allow the safe use of metformin in those who have a low GFR.
Dialysis	<ul style="list-style-type: none"> No current role
AKI (or at risk of AKI)	<p>Review and consider (temporarily) stopping* metformin in those 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) are at risk 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 hypotension or volume depletion in the presence of hypotension or shock, eg severe infection intravascular administration of iodinated contrast drugs (stop metformin on the day of and 2 days after X-ray related intravenous contrast use) co-administration with nephrotoxic drugs, eg non-steroidal anti-inflammatory drugs (NSAIDs) those 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 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>Increased vigilance is needed for the following groups of people who are likely to be at a higher risk 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.

GLP-1 receptor agonists: exenatide (Byetta™ and Bydureon™), liraglutide, lixisenatide, dulaglutide, semaglutide	
eGFR level	Action to be taken
For all	<ul style="list-style-type: none"> Older people: No dose adjustment is required based on age. Therapeutic experience in people ≥75 years of age is limited Paediatric population: The safety and efficacy in children aged up to 18 years have not yet been established. No data are available. Should not be used in people with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. No experience in those with congestive heart failure NYHA class IV and, therefore, not recommended in these people. If pancreatitis is suspected, drug should be discontinued; if confirmed, then should not be restarted. Caution should be exercised in people with a history of pancreatitis.
>60 mL/min/1.73 m²	No renal contraindication to initiation or continuation.
45–60 mL/min/1.73 m²	No renal contraindication to initiation or continuation.
30–45 mL/min/1.73 m²	Byetta™ and lixisenatide to be used 'with caution' in people with creatinine clearance 30-50 mL/min, Bydureon™ should be stopped. Liraglutide, dulaglutide and semaglutide have no renal contraindication to initiation or continuation at standard doses.
<30 mL/min/1.73 m²	Liraglutide, dulaglutide and semaglutide have no renal contraindication to initiation or continuation at standard doses.
Dialysis	No current role
AKI (or at risk of AKI)	<p>Review and consider (temporarily) stopping* in people 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) are at risk of AKI such as: <ul style="list-style-type: none"> acute volume depletion and dehydration eg gastrointestinal upset, stomas, change in diuretic dose operative procedures with a high risk of hypotension or volume depletion in the presence of hypotension or shock, eg severe infection have had previous episodes of AKI. <p>*Duration of stopping GLP-1 receptor agonist should be based on the likely period of risk.</p>

DPP-4 inhibitors: vildagliptin, saxagliptin, sitagliptin, linagliptin, alogliptin	
eGFR level	Action to be taken
For all	<ul style="list-style-type: none"> Older people (≥65 years): In general, no dose adjustment is recommended based on age. Paediatric population: The safety and efficacy of DPP-4 inhibitors in children aged 0 to <18 years have not yet been established. No data are available. No dose adjustments are needed for mild to moderate hepatic impairment. Caution needs to be exercised with alogliptin use in those with severe hepatic impairment. Vildagliptin should not be used in hepatic impairment. Alogliptin and saxagliptin are not recommended in severe hepatic impairment. Only linagliptin is licensed for use in severe hepatic impairment. Acute pancreatitis: DPP-4 inhibitors are associated with risk of developing acute pancreatitis. Caution should be exercised in those with history of pancreatitis. Heart failure: DPP-4 inhibitors do not increase risk of major CV events or risk of hospitalisation for heart failure except saxagliptin, which is contraindicated in heart failure.
>60 mL/min/1.73 m²	No renal contraindication to initiation or continuation.
45–60 mL/min/1.73 m²	eGFR <50 mL/min/1.73 m ² , reduce dose of sitagliptin to 50 mg daily, vildagliptin to 50 mg once daily, alogliptin to 12.5 mg daily and saxagliptin to 2.5 mg daily. No dose reduction needed for linagliptin.
30–45 mL/min/1.73 m²	Reduce dose of sitagliptin to 50 mg daily, vildagliptin to 50 mg once daily, alogliptin to 12.5 mg daily and saxagliptin to 2.5 mg daily. No dose reduction needed for linagliptin. Vildagliptin has limited data and should be used with caution.

<30 mL/min/1.73 m²	<ul style="list-style-type: none"> Reduce dose of sitagliptin to 25 mg daily, alogliptin to 6.25 mg daily and saxagliptin to 2.5 mg daily. No dose reduction needed for linagliptin. Vildagliptin has limited data and should be used with caution.
Dialysis	<ul style="list-style-type: none"> Reduce dose of sitagliptin to 25 mg daily, and alogliptin to 6.25 mg daily. No dose reduction needed for linagliptin. Saxagliptin is not recommended. Vildagliptin has limited data and should be used with caution.

SGLT-2 inhibitors: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	
eGFR level	Action to be taken
For all	<ul style="list-style-type: none"> Older people (≥65 years): In general, no dose adjustment is recommended based on age. Paediatric population: The safety and efficacy of dapagliflozin in children aged up to 18 years have not yet been established. No data are available. Active foot disease (either ulceration with sepsis or ischaemia) avoid initiation and withdraw if this occurs. Diabetic ketoacidosis: permanently discontinue if people develop DKA on treatment.
>60 mL/min/1.73 m²	<ul style="list-style-type: none"> No renal contraindication to initiation or continuation.
45–60 mL/min/1.73 m²	<ul style="list-style-type: none"> Canagliflozin 100 mg daily may be commenced for glucose lowering and reno-protection. Dapagliflozin 10 mg daily may be commenced/continued for heart failure. For other drugs, current licence recommends against initiation (but see recommendations). Continuation of medication should be at the lower dose for canagliflozin and empagliflozin.
30–45 mL/min/1.73 m²	<ul style="list-style-type: none"> Canagliflozin 100 mg daily may be commenced for reno-protection. Dapagliflozin 10 mg daily may be commenced/continued for heart failure. For glucose lowering, current licence recommends against initiation or continuation.
<30 mL/min/1.73 m²	<ul style="list-style-type: none"> Canagliflozin 100 mg daily may be continued for reno-protection until dialysis or renal transplantation. Dapagliflozin 10 mg daily may be commenced/continued for heart failure.
Dialysis	<ul style="list-style-type: none"> No current role
AKI (or at risk of AKI)	<p>Review and consider (temporarily) stopping* in people who:</p> <ul style="list-style-type: none"> have acute major changes in renal function (a fall in eGFR of >10 mL/min/1.73 m² over a period of days or weeks)* are at risk of AKI such as: <ul style="list-style-type: none"> acute volume depletion and dehydration eg gastrointestinal upset, stomas, change in diuretic dose operative procedures with a high risk of hypotension or volume depletion in the presence of hypotension or shock, eg severe infection have had previous episodes of AKI. <p>*Duration of stopping SGLT-2 inhibitor should be based on the likely period of risk.</p>

Table 6: Glucose-lowering therapies – current licensing based on eGFR and cardiorenal protection

Drug	Class of drug	Renal impairment – CKD stage and eGFR (mL/min/1.73 m ²)					
		1 eGFR ≥90	2 eGFR 60–89	3a eGFR 45–59	3b eGFR 30–44	4 eGFR 15–29	5 eGFR <15
Metformin	Biguanide				Reduce dose to 500 mg twice daily	eGFR may underestimate in obesity, potential role for 500 mg	
Gliclazide	Sulphonylurea	Monitor CBG	Monitor CBG	Monitor CBG	Dose reduction advised Monitor CBG	Off licence – high risk of hypoglycaemia; monitor CBG	
Repaglinide	Meglitinide	Monitor CBG	Monitor CBG	Monitor CBG	Monitor CBG	Dose reduction advised Monitor CBG	Dose reduction advised Monitor 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 25 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			
Exenatide MR	GLP-1 agonist			Stop if CrCl** <50 mL/min			
Liraglutide	GLP-1 agonist						
Dulaglutide	GLP-1 agonist						
Semaglutide (oral/injectable)	GLP-1 agonist						
Dapagliflozin†	SGLT-2i			Do not initiate, maintain dose at 10 mg daily	May initiate and continue for treatment of heart failure	Limited experience for treatment of heart failure.	
Canagliflozin‡	SGLT-2i			Do not initiate, reduce dose to 100 mg daily	May initiate at 100 mg and/or continue for reno-protection	Continue at 100 mg for reno-protection	
Empagliflozin	SGLT-2i			Do not initiate, reduce dose to 10 mg daily			
Ertugliflozin	SGLT-2i			Do not initiate			
Insulin					Dose reduction may be needed	Dose reduction should be needed	Dose reduction should be needed

CBG = capillary blood glucose. Note that **Sick day guidance** (see Appendix A, p89) applies to metformin, all SGLT-2 inhibitors and GLP-1 agonists

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

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

†Dapagliflozin can be initiated and continued for treatment of heart failure without reference to renal function

‡Canagliflozin can be initiated for reno-protection down to an eGFR of 30 mL/min/1.73 m² and be continued thereafter until the onset of dialysis or transplantation

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 kidney disease (DKD) 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 people with CKD stage 3b and below who are on insulin, and whose HbA1c is 58 mmol/mol (7.5%) or below, a reduction of insulin doses should be considered (Grade 1C).
- 4 People 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 people 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 people 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 people with CKD stages 3–5. This regimen, however, may be useful in individuals 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 people 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 people with DKD?
- 2 Is there a role for 50:50 mixed insulins in people with DKD and progressive renal disease?
- 3 Is there a role for continuous subcutaneous insulin infusion (CSII) in people with DKD and progressive renal disease?
- 4 Is there a role for biosimilars or insulin–GLP-1 analogue mixtures in people 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 people with CKD stage 3b and below who are on insulin and whose HbA1c is 58 mmol/mol (7.5%) or below, whose insulin dose has been reduced.
- 2 The proportion of insulin-treated people 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 people who have an eGFR of <60 mL/min/1.73 m² (and <45 mL/min/1.73 m²) if on insulin therapy in combination with sulfonylureas, where HbA1c values below 53 mmol/mol (7.0%).

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.⁴⁸ 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).⁴⁹ In people with type 2 diabetes, renal gluconeogenesis, glucose uptake and renal glucose reabsorption are all increased.⁵⁰ Furthermore, the relative increase in renal gluconeogenesis is significantly greater than the increase seen in hepatic gluconeogenesis (300% versus 30%).⁴⁸

In healthy individuals, 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.⁵¹ Renal insulin clearance is around 200 mL per minute: higher than normal GFR due to the contribution of renal tubular secretion.⁵² 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 their important role in the metabolism of exogenous insulin.⁵³

Glucose homeostasis in people with CKD

Insulin resistance is common in people with CKD. A number of mechanisms have been suggested to explain this, including the presence of 'uraemic toxins',⁵⁴ excess parathyroid hormone due to deficiency of active 1,25-dihydroxyvitamin D,⁵⁵ or anaemia⁵⁶ 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;⁵⁷ the fact that the administration of active vitamin D (1,25-dihydroxyvitamin D) may enhance insulin sensitivity;⁵⁸ and the fact that improved glucose uptake is seen following the correction of anaemia with erythropoietin.⁵⁹

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.^{60,61}

Insulin secretion can also be impaired in people with uraemia. Metabolic acidosis seen in renal impairment may lead to the suppression of insulin release,⁶² 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.⁵⁸

Insulin therapy in people with CKD stages 1–3

Many oral hypoglycaemic therapies are contraindicated in CKD or may be ineffective in people 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 DKD, resistance to the effects of insulin predominates and may worsen, leading to a greater requirement for insulin.⁶³ Indeed, the presence of micro- or macroalbuminuria is noted to be strongly associated with insulin resistance.⁶⁴ Insulin requirements, therefore, are frequently higher in early DKD, 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 $<60 \text{ mL/min/1.73 m}^2$, compared with when the GFR is $>90 \text{ mL/min/1.73 m}^2$.^{65–67}

The use of insulin therapy in people with mild or moderate DKD 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 participants with type 2 diabetes and coronary artery disease (CAD), and monitored albumin:creatinine ratio (ACR) over 5 years.⁶⁸ 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.⁶⁹ After 4 years, people 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 people with DKD, but relevant studies have been small and short term. One study of insulin pharmacokinetics in a small number of people with type 1 diabetes with and without nephropathy showed that glucose profiles were more responsive to analogue insulin compared with human insulin.⁷⁰ In people 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.⁷¹

A recent meta-analysis of 6-month pooled data from the EDITION 1, 2 and 3 trials ($n=2,496$) examining the use of insulin glargine U300 (Toujeo®) in people with CKD in comparison with insulin glargine U100 has been reported. This suggested that there was a reduced risk of nocturnal or severe hypoglycaemia by 24% (RR 0.76; 95% CI 0.62–0.94), suggesting a modest benefit of insulin glargine U300 over insulin glargine U100.⁷²

The BRIGHT study was an open label parallel trial comparing glargine U300 with insulin degludec U100 and examined glycaemic effects according to renal status. There was some suggestion of greater reduction in HbA1c with less hypoglycaemia in people on glargine U300, but the study design limits any firm conclusions being drawn.⁷³

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

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

In people 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.⁵⁶ In addition, uraemia-induced anorexia and weight loss may also occur, leading to significant reductions in insulin requirements. 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.⁷⁴ 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.^{75,76}

The use of insulin therapy or the type of insulin therapy has not been subjected to randomised study in people 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 people with a GFR of <45 mL/min/1.73 m² resulted in lower rates of hypoglycaemia, without compromising control of glycaemia.⁷⁷ A further study suggests that the use of insulin glargine in people with type 2 diabetes and renal impairment may lead to improved control.⁷⁸ This study examined 89 people 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 individuals 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 people with renal impairment suggested that the pharmacokinetic properties of insulin degludec were preserved in people with renal impairment, including in those with end-stage kidney disease,⁷⁹ suggesting that no dose adjustment is needed with degludec in people with significant renal impairment.

Insulin therapy in people with end-stage kidney disease

Insulin therapy in people 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.⁸⁰

The use of insulin in combination with a sulfonylurea for people 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.⁸¹

3 Sulfonylureas

Recommendations

- 1 People 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 those who have an estimated glomerular filtration rate (eGFR) of $<45 \text{ mL/min/1.73 m}^2$, CBG monitoring should be mandatory (Grade 2B).
- 2 Gliclazide and glipizide are metabolised in the liver and are therefore the preferred SUs for people 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 people with an eGFR of $<45 \text{ mL/min/1.73 m}^2$ (Grade 2B).
- 4 We suggest that SUs should be avoided alongside insulin in people with an eGFR of $<45 \text{ mL/min/1.73 m}^2$, 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 person's eGFR is $<30 \text{ mL/min/1.73 m}^2$, 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 people with CKD, and we suggest that they should be avoided in such individuals (Grade 2B).

Areas that require further research

- 1 What is the relationship between SUs and hypoglycaemia (with or without concomitant insulin therapy) in people with CKD?
- 2 What is the SU-related mortality in people 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 people with CKD who are on SUs and who regularly monitor their CBG.
- 2 The proportion of people with an eGFR of $<30 \text{ mL/min/1.73 m}^2$ who are on SUs and who regularly monitor their CBG.
- 3 The proportion of people 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 people with an eGFR of <60 (and <45) mL/min/1.73 m^2 who are on SUs, and the dosage used.
- 5 The proportion of people with an eGFR of <60 (and <45) mL/min/1.73 m^2 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 people with CKD who are on SUs and other drugs.

Evidence base

SUs work by closing adenosine triphosphate (ATP)-sensitive potassium channels in 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 people with end-stage kidney disease, including those on dialysis, may predispose them to a risk of hypoglycaemia.

SUs should be used with caution in those who have a glucose-6-phosphate dehydrogenase (G6PD) deficiency, and should not be used in people with type 1 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)⁸² and risk of hypoglycaemia,⁸³ which is even higher in people 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 people 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 people with type 2 diabetes on haemodialysis remains off licence.

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

Hypoglycaemia is more common in people with CKD, due to reduced oral intake and decreased insulin clearance via the kidneys. In a retrospective cohort analysis of people 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).⁸⁴

Bodmer *et al*⁸³ 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% 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 people 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 people who were treated with SUs than with pioglitazone (severe 0% v 2%, $p < 0.01$; moderate 32% v 10%, $p < 0.01$).⁸⁵

The CAROLINA trial compared the effect of linagliptin vs glimepiride on CV outcomes in people with type 2 diabetes and relatively normal kidney function (mean (SD) eGFR was 76.5 (19.7)–77.0 (19.8) and <20% had eGFR <60 mL/min/1.73 m²).⁸⁶ It did not demonstrate any significant difference between the two drugs according to primary outcome (3-point MACE), or secondary outcome (3-point MACE plus hospitalisation for unstable angina). However, people treated with glimepiride had more hypoglycaemic episodes (115 vs 38% HR 0.23; 95% CI 0.21–0.26). It is not clear from the study if the hypoglycaemic episodes were more likely to happen in those with impairment of renal function. It has, however, provided some reassurance around concerns around CV outcomes in SUs.

Hypoglycaemia is underreported due to testing limitations, legal implications for driving and impaired warning signs. Due to the increased cardiovascular disease burden in people 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 people 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 people in both groups had microalbuminuria and the nephropathy progression rate over 5 years was the same (at 23%).⁸⁵

In theory, treating people with CKD with a combination of an SU and insulin 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.⁸⁷

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),⁸⁸ but it is not uncommon for it to be prescribed off licence in severe CKD. Ninety-five per cent 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)).⁸⁹ 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.⁸⁵

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.⁹⁰

Glimepiride was used as an active comparator against linagliptin in CAROLINA (see above), but people with impaired kidney function were under-represented in this study design. The study provided evidence that glimepiride was safe to use, which had been lacking previously. The concern regarding increased risk of hypoglycaemia with glimepiride treatment remains (in this study 77% relative risk increase) and has to be balanced against the cost argument, especially in people with advanced kidney disease.⁸⁶

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 end-stage kidney disease. Glipizide is unlikely to be dialysed by either peritoneal dialysis or haemodialysis.⁹¹

The efficacy and safety of sitagliptin (25–50 mg based on the individual's eGFR) and glipizide (2.5–10 mg based on the individual's response) monotherapy in people 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; $p=0.001$).⁹¹ Symptoms of hypoglycaemia cannot be relied upon in people with CKD, as hypoglycaemic awareness is often reduced; hence, CBG monitoring is necessary.

Tolbutamide

Tolbutamide is contraindicated in people with severe renal impairment. It is unlikely to be dialysed by either peritoneal dialysis or haemodialysis.⁹²

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 people with CKD.^{93,94}

The use of glibenclamide in people with decreased renal function should be limited and is contraindicated in those with severe end-stage kidney disease (CDK stage 5).⁹⁵

4 Meglitinides

Recommendations

- 1 Meglitinides can be considered for use in people with type 2 diabetes and chronic kidney disease (CKD) as a monotherapy (repaglinide) or in addition to metformin (nateglinide and repaglinide) if other drugs are not tolerated (Grade 2C).
- 2 In people 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 people with CKD stages 4 and 5 who are on dialysis (Grade 2C). In these individuals, 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 people with type 2 diabetes and CKD.
- 2 The efficacy and safety of meglitinides in people 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 people with type 2 diabetes and CKD.

Audit standards

- 1 The percentage of people with type 2 diabetes and CKD who use meglitinides as mono or dual therapy, across the range of eGFRs.
- 2 The percentage of people 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 people with an eGFR of $<30 \text{ mL/min/1.73 m}^2$ 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 people 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).^{96,97} The main side effect of nateglinide and repaglinide is hypoglycaemia. Both drugs 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 people 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 people with CKD, due to the lower risk of hypoglycaemia.⁹⁸

Nateglinide is metabolised in the liver, but its main metabolite retains a glucose-lowering effect.⁹⁶ Renal impairment does not significantly alter the excretion of nateglinide, and it is licensed for use in people with all stages of CKD. When renal function is impaired, however, nateglinide's main metabolite is accumulated and significantly cleared by dialysis.^{99,100} It is recommended that the dose of nateglinide is reduced in people with advanced end-stage kidney disease (CKD stage 5).

A retrospective subgroup analysis from all completed nateglinide studies in high-risk individuals (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 individuals. The risk of documented moderate and severe hypoglycaemia increased by 0.8% in people with CrCl of <60 mL/min, compared with people with normal renal function.¹⁰¹ A 2-week study of nateglinide in people with renal transplant demonstrated a significant improvement in postprandial hyperglycaemia; better insulin response following a standardised meal; and a good side-effect profile.¹⁰²

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 people with type 2 diabetes who also have CKD. The incidence of hypoglycaemia is comparable to that of gliclazide.¹⁰³ Repaglinide is metabolised in the liver and <8% of it is excreted unchanged via the kidneys. In people with advanced end-stage kidney disease (CKD stage 5), the concentration of repaglinide does increase, but at a level that is not considered to be metabolically relevant.⁹⁷ Haemodialysis does not change clearance of repaglinide.¹⁰⁴

The Multinational Repaglinide Renal Study Group conducted an open-label safety and efficiency study in people 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 ≤ 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 people who had detectable repaglinide in fasting bloods increased with advancing renal failure, but the dose was too low to be considered metabolically relevant.¹⁰⁵

Cardiovascular safety of meglitinides

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 people from the Danish National Registry who were followed for up to 9 years.¹⁰⁶

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 people, 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.¹⁰⁷ This is in contrast with Ristic *et al*,⁹⁸ 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 people 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 people with advanced CKD (eGFR of <30 mL/min/1.73 m²), with repaglinide having preferred metabolism to nateglinide. See [Table 5](#) for advice for healthcare workers who are managing type 2 diabetes with nateglinide and repaglinide in people who have CKD.

5 Metformin

Recommendations

- 1 Metformin can be used in those 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 people who are obese. 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 person has acute kidney injury (AKI). Everyone who is treated with metformin should be given sick day guidance, which should be reiterated at every medication review ([Appendix A](#)) (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 people with diabetes and chronic kidney disease (CKD)?
- 2 Can metformin be used safely in people 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 people with CKD who are on metformin?

Audit standards

- 1 The proportion of people with CKD on metformin who have received sick day guidance ([Appendix A](#)).
- 2 The proportion of people in whom metformin is stopped during acute illness, but in whom metformin is restarted on recovery.
- 3 The proportion of people 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 people with diabetes

Metformin has been used as a first-line oral drug for people 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.¹⁰⁸ It is an inexpensive, safe and very effective drug 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 people 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 people *the benefits of metformin greatly outweigh the risks of serious complications.*

Benefits of metformin therapy in people with diabetes

Metformin has achieved a strong evidence base for improving outcomes in people 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.^{109,110} In the UKPDS, 10 people needed to be treated with metformin (with an average fall in HbA1c of 8–9 mmol/mol (0.9%)) for 10 years in order to prevent one diabetes-related endpoint.

A recent systematic review suggests that metformin use in moderate CKD (eGFR 30–60 mL/min/1.73 m²) confers a mortality benefit of 22% (HR 0.78; 95% CI 0.63–0.96).¹¹¹ Examination of a cohort of people who were part of the TREAT (use of aranesp in CKD study) also suggested that metformin use was independently associated with a reduced risk of all-cause mortality (HR 0.49; 95% CI 0.36–0.69) and cardiovascular death (HR 0.49; 95% CI 0.32–0.74).¹¹² On the other hand, examination of the SAVOR-TIMI cohort of 12,156 people showed that while metformin use was associated with lower rates of all-cause mortality, this was less apparent in those with moderate to severe CKD.¹¹³

A further study of 175,296 new users of metformin or a sulfonylurea monotherapy found that metformin monotherapy was associated with a lower mortality compared with sulfonylurea monotherapy across all ranges of eGFR (HR ranging from 0.59 to 0.80), with the greatest risk difference in the eGFR category 30–44 mL/min/1.73 m² (12.1 fewer

deaths/1,000 person-years; 95% CI 5.2–19.0).¹¹⁴ In a retrospective cohort of 174,882 US veterans using metformin or sulfonylurea monotherapy and eGFR < 60 mL/min/1.73 m², the cause-specific adjusted hazard ratio for major adverse cardiovascular events (MACE) for metformin was 0.80 (95% CI 0.75–0.86) compared with sulfonylureas.¹¹⁵

A survey of anti-diabetic medication prescription in over 38,000 people with CKD suggests that metformin is underused in people with mild to moderate CKD. It found that over a third of people eligible for metformin with mild CKD were not being prescribed the drug, possibly due to perceived risks in CKD.¹¹⁶

Vascular risks in people 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 person has diabetes, and this is further increased if a person 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 people with CKD

Vitamin B₁₂ deficiency may be common in people with diabetes and CKD, and malabsorption of B₁₂ with metformin has been considered to be one of the explanations for this finding.^{117,118} Although people with peripheral neuropathy might be especially likely to have B₁₂ deficiency, the impact of this deficiency in people with DKD who are being treated with 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.¹¹⁹ 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.^{120–122}

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 people 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.^{123,124}

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.¹²⁵ 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.¹²⁶ 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 people 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).¹²⁷ A further recent analysis of a community based cohort of 75,413 people showed that metformin was not associated with an increased risk of acidosis in people with eGFRs above 30 mL/min/1.73 m², but below this level, risk for acidosis was increased (HR 2.07; 95% CI, 1.33–3.22).¹²⁸

Current consensus and many reviews of the cases and the literature suggest that metformin may be a bystander when people with diabetes present with lactic acidosis.^{129,130} Many consider that this is particularly the case for those with diabetes and 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 people with an eGFR of <60 mL/min/1.73 m² were receiving metformin.¹³¹ 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 people with metformin-associated lactic acidosis (MALA).¹³²

Balancing the risk of MALA in people with CKD

In summary, for most people 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 people 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.¹³³ In recognising that there may be subgroups of people who are at higher risk of lactic acidosis (not just impaired renal function), however, the practical advice for clinicians and people contained in [Table 5](#) is relevant and in general supports the ongoing

use of metformin for people with stable CKD stage 3 and for some with CKD stage 4, albeit with increased vigilance and dose reductions down to 1,000–500 mg/day.

6 Thiazolidinediones: Pioglitazone

Recommendations

- 1 We recommend that people 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 someone has heart failure or macular oedema (Grade 1B).
- 3 Caution is required when commencing treatment in people who have evidence of fluid overload. These individuals should be monitored for fluid retention initially after 2 weeks, and 3–6-monthly thereafter (Grade 1C).
- 4 We advise that people 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 people who have an increased risk of hip fractures (Grade 1C).
- 6 Consider discontinuing pioglitazone in people who develop hip fractures while they are on pioglitazone (Grade 1D).
- 7 Do not start pioglitazone in people who have known bladder cancer (Grade 1B).
- 8 We suggest the discontinuation of pioglitazone in people 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 people who are on pioglitazone, in comparison with other therapies in people who have type 2 diabetes and CKD.
- 4 The efficacy and safety of pioglitazone as a third-line oral therapy in people with type 2 diabetes and CKD.
- 5 The efficacy and safety of pioglitazone use with background insulin in people with type 2 diabetes.
- 6 The potential cardiovascular benefit of pioglitazone treatment in people with type 2 diabetes and chronic heart failure, where fluid retention is controlled by diuretics.
- 7 The rate of renal function decline in people with type 2 diabetes who are taking pioglitazone.
- 8 The role of pioglitazone in post-transplantation diabetes with CKD.

Audit standards

- 1 The proportion of people with type 2 diabetes and CKD who are taking pioglitazone (with or without insulin) across the range of eGFRs.
- 2 The proportion of people 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 people who are taking pioglitazone, across the range of eGFRs.
- 4 The proportion of people 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 people who have type 2 diabetes and CKD, across the range of eGFRs.
- 6 The rate of heart failure that requires hospitalisation among pioglitazone-treated people 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 people with type 2 diabetes.⁴ 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.¹³⁴ 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 people 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.¹³⁵ The PROactive study, which randomised 2,605 people 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 placebo (HR 0.84; 0.72–0.98; $p=0.027$).¹³⁶ 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);^{137,138} blood pressure (BP) (small, but sustained reduction of systolic and diastolic BP by 7 mmHg and 5 mmHg respectively);¹³⁹ and inflammatory mediators involved in the atherosclerotic process.¹⁴⁰ This is particularly relevant to people with CKD where cardiovascular events are the main causes of morbidity. A subgroup analysis of 506 people 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% CI 0.45–0.98).¹⁴¹

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 people aged 50–75 years found no difference in the primary composite outcome between the groups.¹⁴² 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 participants had a serum creatinine of less than 132 $\mu\text{mol/L}$ 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%, $p<0.01$).^{142,143}

Pioglitazone's effect on renal function and albuminuria

TZDs lower microalbuminuria and proteinuria in animal models and people with CKD with and without diabetes.^{144–147} It can be speculated that protein leak reduction is an indirect, BP-mediated effect. In a placebo-controlled, randomised study in 1,199 people 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.¹⁴¹ Whether the reduction of protein leak can be translated into a slower decline of renal function in people with DKD remains to be studied.

Pioglitazone's effect in people who are on maintenance haemodialysis or peritoneal dialysis

Several randomised controlled trials of pioglitazone as a single drug, or in combination with insulin / other oral antidiabetic drugs, demonstrated its benefits to diabetes control, lipid profile and inflammatory markers in people with type 2 diabetes who are on dialysis.^{148,149,150} In a retrospective analysis of 5,290 people with diabetes who were on dialysis, TZDs reduced the risk of all-cause mortality by 35% (HR 0.65; 95% CI 0.48–0.87)¹⁵¹ but concomitant insulin treatment abolished the benefits of TZDs.

Areas of concern

Pioglitazone increases the odds ratio (OR) for fluid retention (OR 2.22 (1.96–2.52)), which precludes its use in people with heart failure. People 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.¹³⁵ 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 people with diabetic retinopathy. Fong *et al* analysed data from 170,000 people 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.¹⁵²

The ADOPT study raised an issue of the association between cortical bone fractures and rosiglitazone treatment.¹⁵³ 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.¹⁵⁴ This is of even greater concern in people with DKD 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 people (HR 1.23; 95% CI 1.09–1.39; I^2 0%).¹⁵⁵ 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.¹⁵⁶ A subsequent definitive study, however, on the relationship between bladder cancer and pioglitazone, based on Cohort and nested case-control analyses among people with diabetes from the Kaiser Permanente Database,¹⁵⁷ dismissed an association between bladder cancer and pioglitazone. Further reassurance came from a study that included over a million people.¹⁵⁸ 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.¹⁵⁹ 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.⁴ In 2016, ABCD suggested the need for NICE to undertake an evidence and recommendation review.¹⁶⁰ A more recent meta-analysis could not demonstrate any clear link with pioglitazone and bladder cancer.¹⁶¹ Despite this conflicting evidence, Medicines and Healthcare products Regulatory Agency (MHRA) guidance from 2014 has not been updated to reflect this.¹⁶²

Pioglitazone is one of few oral glucose-lowering drugs that are currently licensed for use in people with advanced CKD (eGFR of <30 mL/min/1.73 m²). It is inexpensive and efficient, and has a low risk of hypoglycaemia. It can be considered for the treatment of type 2 diabetes in people who have CKD of all stages after the exclusion of heart failure and macular oedema, and after fracture risk has been considered. People should be carefully and regularly monitored for fluid retention (see [Table 5](#)).

7 Dipeptidyl peptidase-4 inhibitors

Recommendations

- 1 We recommend that people with type 2 diabetes and chronic kidney disease (CKD) of all stages are suitable 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 People 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 suggest that DPP-4 inhibitors (except saxagliptin) are associated with an excess risk of hospitalisation for people 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 pioglitazone that is also licensed for use in people 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 people with type 2 diabetes.
- 3 A head-to-head comparison between various DPP-4 inhibitors with regard to HbA1c reduction in people with type 2 diabetes and CKD.
- 4 The mechanisms that underlie the potential differential effects of DPP-4 inhibitors on albuminuria and their relationship with glucose lowering.

Audit standards

- 1 The proportion of people 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 people 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 people 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 people 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 people 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 people with type 2 diabetes and CKD, across the range of eGFRs.

- 7 The incidence of hospitalisation for heart failure of people 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 people with progressive renal impairment.

Areas of concern

- 1 The potential for heart failure in people who have a high cardiovascular risk and CKD who are using saxagliptin or alogliptin.

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 people with type 2 diabetes and mild-to-severe renal impairment.^{163–168}

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 people 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 people 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 person's degree of renal impairment.^{169–171}

With an eGFR of 30–45 mL/min/1.73 m² dose reduction to 50 mg once daily is advised, and to 25 mg once daily if eGFR is less than 30 mL/min/1.73 m².

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.¹⁷⁰ For people with severe renal impairment (CrCl of <30 mL/min) or with end-stage kidney disease (ESKD) 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*,¹⁷² albuminuria was a secondary endpoint in 82 participants 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 UACR from 8.61 ± 10.6 to 3.73 ± 5.44 mg/mmol (76.2 ± 95.6 to 33.0 ± 48.1 mg/g), along with a slight decrease 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)).¹⁷³ 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 person's baseline eGFR. There was no increased risk for hospitalisation for heart failure seen in the sitagliptin treated group. In the subset of participants who had urinary albumin to creatinine ratio (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 -0.0203 mg/mmol (-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 people with CKD stage 3, a moderate increase in exposure of about 1.7-fold was observed compared with a control group. Exposure in people with type 2 diabetes and CKD stages 4 and 5 was increased by about 1.4-fold compared with people with type 2 diabetes and normal renal function. Steady-state predictions for the area under the curve (AUC) of linagliptin in people with ESKD indicated an exposure that is comparable with that of people 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 people who are on MHDx.¹⁷⁴

Linagliptin pharmacokinetics was studied under single-dose and steady-state conditions in people with mild, moderate and severe renal impairment. The accumulation half-life of linagliptin ranged from 14–15 hours in individuals 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 people with type 2 diabetes.¹⁷⁵

In another trial,¹⁷⁶ treatment with linagliptin or a placebo followed by glimepiride was studied in people 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 people 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.¹⁶⁷

Albuminuria reduction with linagliptin was studied in a randomised, double-blind, placebo-controlled trial (duration 24–52 weeks) in 2012.¹⁷⁷ The inclusion criteria were: persistent albuminuria (defined as UACR 3.39–339 mg/mmol [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 participants were treated with linagliptin and 59 participants 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 people, 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.¹⁷⁸ 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.¹⁷⁹

The Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus (CARMELINA),¹⁸⁰ a study of people at high cardiovascular and renal risk, involved 6,979 people over a median follow-up of 2.2 years. It included people with type 2 diabetes, haemoglobin A1c of 6.5% to 10.0%, high CV risk (history of vascular disease and UACR >22.6mg/mmol (>200 mg/g), and high renal risk (reduced eGFR and micro- or macroalbuminuria). People were randomised to receive linagliptin, 5 mg once daily (n = 3,494), or placebo once daily (n = 3,485) added to usual care. Other glucose-lowering medications or insulin could be added based on clinical need and local clinical guidelines. Primary outcome was time to first occurrence of the composite of CV death, non-fatal myocardial infarction, or non-fatal stroke. Secondary outcome was time to first occurrence of adjudicated death due to renal failure, ESKD, or sustained 40% or higher decrease in eGFR from baseline.

Primary outcome occurred in 434 of 3,494 (12.4%) and 420 of 3,485 (12.1%) in the linagliptin and placebo groups, respectively, (absolute incidence rate difference, 0.13 [95% CI, –0.63–0.90] per 100 person-years) (HR, 1.02; 95% CI 0.89–1.17; p <0.01 for non-inferiority). The kidney outcome occurred in 327 of 3,494 (9.4%) and 306 of 3,485 (8.8%), respectively (absolute incidence rate difference, 0.22; 95% CI –0.52 to 0.97 per 100 person-years) (HR, 1.04; 95% CI 0.89–1.22; p=62). Progression of albuminuria occurred less frequently in the linagliptin group (763/2,162 = 35.3%) than the placebo group (819/2,129 = 38.5%) – HR 0.86; 95% CI 0.78–0.95; p=0.03. Adverse events occurred in 2,697 (77.2%) and 2,723 (78.1%) people in the linagliptin and placebo groups; 1,036 (29.7%) and 1,024 (29.4%) had one or more episodes of hypoglycaemia; and there were 9 (0.3%) vs 5 (0.1%) events of adjudication-confirmed acute pancreatitis.

It concluded that among adults with type 2 diabetes and high CV and renal risk, linagliptin added to usual care compared with placebo added to usual care resulted in a noninferior risk of a composite CV outcome over a median 2.2 years.

The CAROLINA® (CARDiovascular Outcome trial of LINAgliptin) Trial, an active-comparator cardiovascular (CV) outcome trial, evaluated the long-term CV safety of once-daily linagliptin (5 mg) compared with the sulphonylurea (SU) glimepiride, on top of standard of care (SOC)

in 6,033 adults with early type 2 diabetes and increased CV risk or established cardiovascular disease (CVD).^{181,182,183} Results from this trial demonstrated that, with similar overall levels of glucose control:

- 1 there was no increased CV risk with linagliptin compared with glimepiride ($p < 0.0001$).
- 2 there was no increased risk for hospitalisation for heart failure with linagliptin compared with glimepiride
- 3 the risk of hypoglycaemia was significantly lower with linagliptin compared with glimepiride ($p < 0.0001$).
- 4 linagliptin was associated with a reduction in body weight relative to glimepiride (an average between group difference of -1.5 kg).
- 5 after a median follow-up of 6.3 years, an overall safety profile of linagliptin was consistent with previous data, with no new safety signals observed.

Results from the CAROLINA trial support the long-term overall CV safety profile of linagliptin in people with type 2 diabetes.

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 2-fold in people with mild, moderate and severe renal impairment, respectively, compared with healthy individuals. The AUC of the metabolites LAY151 (the main metabolite) and BQS867 increased on average by about 1.5-, three- and seven-fold in people with mild, moderate and severe renal impairment, respectively. LAY151 concentrations were approximately two- to three-fold higher than in people with severe renal impairment.¹⁸⁴

In a randomised clinical trial of vildagliptin and sitagliptin in people 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.¹⁸⁵

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 people with mild renal impairment (CrCl of ≥ 50 mL/min). In people with moderate or severe renal impairment or those with ESKD, the recommended dosage is 50 mg once daily.

A retrospective meta-analysis of prospectively adjudicated cardiovascular events that involved 17,446 people 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 people and 85 (1.20%) comparator-treated people, with an HR of 0.82 (95% CI 0.61–1.11). Confirmed heart failure events were reported in 41 (0.43%) vildagliptin-treated people and 32 (0.45%) comparator-treated people, 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 individuals, such as those with congestive heart failure and/or moderate or severe renal impairment.¹⁸⁶

Alogliptin

The efficacy and safety of the recommended doses of alogliptin was investigated separately in a subgroup of people with type 2 diabetes and severe renal impairment / ESKD in a placebo-controlled study (59 people were treated with alogliptin and 56 with a placebo for 6 months). Alogliptin use in the subgroup was found to be consistent with the profile obtained in people with normal renal function. Furthermore, the pharmacokinetic profile of a single dose of alogliptin was evaluated in people with renal impairment and in healthy volunteers.¹⁸⁷ Compared with healthy volunteers, an approximate 1.7-fold increase ($p=0.002$) in the alogliptin total plasma AUC was observed in people with mild renal impairment. In people with moderate and severe renal impairment and ESKD, 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 people 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 people with severe renal impairment (CrCl of <30 mL/min) including ESKD, the dosage should be reduced to 12.5 mg once daily. Fujii *et al*¹⁸⁸ evaluated the efficacy and safety of alogliptin 6.25 mg once daily in 30 people 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 individuals. 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 people 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 participants' 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.¹⁸⁹ Post-hoc analysis of the EXAMINE study showed that, although there was a sign of excess heart failure in the alogliptin group in people 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 people 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 people with type 2 diabetes or recent acute coronary syndrome (ACS), or worsen heart failure outcomes in people with pre-existing heart failure.

Saxagliptin

A single-dose, open-label study¹⁹⁰ was conducted to evaluate the pharmacokinetics of a 10 mg oral dose of saxagliptin in people with varying degrees of chronic renal impairment, compared with people with normal renal function. The study included people 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 people with ESKD 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 those 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 people with normal renal function. Because increases of this magnitude are not clinically relevant, dose adjustment in people with mild renal impairment is not recommended.

In people with moderate or severe renal impairment or in those with ESKD 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 people with normal renal function. The dosage should be reduced to 2.5 mg once daily in people with moderate or severe renal impairment. Data on the experience of people with severe renal impairment are very limited. Therefore, saxagliptin should be used with caution in this population. Saxagliptin is not recommended for people with ESKD 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), people 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 person's renal function. People 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.¹⁹¹ 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.¹⁹² 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 person's degree of renal disease.¹⁹³

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 people 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.^{191,193} Thus, although no overall increase in major adverse cardiovascular events (MACE) was reported, the SAVOR-TIMI 53 trial showed a significant increase in the rate of hospitalisation for unexpected heart failure of 27%.

8 Sodium glucose co-transporter-2 inhibitors

Recommendations

- 1 There are currently four sodium glucose co-transporter-2 (SGLT-2) inhibitors licensed for glucose lowering in people with type 2 diabetes in the UK. The licences state that initiation of dapa-, empa- and ertugliflozin should only take place when the eGFR is >60 mL/min/1.73 m². For dapagliflozin and ertugliflozin, the drug can be continued at its higher dose down to an eGFR of >45 mL/min/1.73 m², while empagliflozin should be reduced to its lower dose. For glucose lowering, canagliflozin can be initiated at the lower dose of 100 mg once daily down to an eGFR of >45 mL/min/1.73 m², but should only be uptitrated to 300 mg once daily in people with an eGFR >60 mL/min/1.73 m². None of the SGLT-2 inhibitors are licensed for glucose lowering in people with an eGFR <45 mL/min/1.73 m².
- 2 Canagliflozin is also licensed for the treatment of diabetic kidney disease as an add-on to standard of care (eg ACE-inhibitors or ARBs) where the initiation is at the lower dose of 100 mg once daily. In people for whom further improvement in HbA1c is needed, this dose can be increased to 300 mg once daily if the eGFR is >60 mL/min/1.73 m². If the eGFR is lower then the dose of canagliflozin should remain at 100 mg once daily and addition of other glucose-lowering therapies is recommended. Canagliflozin should not be initiated if the eGFR is <30 mL/min/1.73 m² but can be continued until renal replacement therapy in those already being prescribed this agent.
- 3 There is clinical trial evidence that empagliflozin and canagliflozin reduce major cardiovascular events in people with type 2 diabetes who are at high cardiovascular risk and that these benefits are seen in people with an eGFR ≥ 30 mL/min/1.73 m² (Grade 1A).
- 4 There is clinical trial evidence that empagliflozin, canagliflozin and dapagliflozin significantly reduce renal composite endpoints in people with type 2 diabetes down to an eGFR of ≥ 30 mL/min/1.73 m² (Grade 1A).
- 5 There is clinical trial evidence that all four SGLT-2 inhibitors significantly reduce the development and progression of heart failure in people with type 2 diabetes, with one trial of empagliflozin including individuals down to an eGFR ≥ 20 mL/min/1.73 m² (Grade 1A).
- 6 There is clinical trial evidence that canagliflozin 100 mg once daily reduces hard renal endpoints (and cardiovascular endpoints) in people with type 2 diabetes who have an eGFR of 30–90 mL/min/1.73 m² and an albumin:creatinine ratio of 33.9–565 mg/mmol (300–5,000 mg/g) (Grade 1A).
- 7 There is clinical trial evidence that dapagliflozin 10 mg once daily reduces a composite cardiorenal outcome, which includes $>50\%$ decline in eGFR, ESKD and renal death in people with type 2 diabetes who have an eGFR of 25–75 mL/min/1.73 m² and a UACR of 22.6–565 mg/mmol (200–5,000 mg/g) (Grade 1A).
- 8 It is likely that the beneficial effects of SGLT-2 inhibitors are present for all members of the class, extend to an eGFR of 25 mL/min/1.73 m² and are independent of glucose lowering (Grade 1B).
- 9 We therefore recommend the consideration of SGLT-2 inhibitors in all individuals with type 2 diabetes with an eGFR ≥ 30 mL/min/1.73 m², irrespective of glycaemic control, recognising that this is currently off-licence practice. For those with established

proteinuria, canagliflozin 100 mg once daily is the preferred drug and dose based on its licence (Grade 1A).

- 10 Where individuals are already receiving treatment with insulin or sulfonylureas, a reduction in dose of these drugs should be considered, so as to reduce the risk of hypoglycaemia (Grade 1A). Switching people to an SGLT-2 inhibitor from another glucose-lowering class (for example, where the HbA1c is already at target), especially those on insulin, should involve a specialist diabetes service.
- 11 The initiation of SGLT-2 inhibitors in people who have active foot disease (ulceration, infection, sepsis and ischaemia) should be avoided and these agents should be withdrawn in people who develop active infected and/or vascular foot complications while on treatment. SGLT-2 inhibitors should only be reinstated after foot problems have fully resolved and following discussion with the multidisciplinary foot team (Grade 1B).
- 12 SGLT-2 inhibitors should be permanently withdrawn in people who develop diabetic ketoacidosis (DKA) while receiving a SGLT-2 inhibitor.
- 13 We do not recommend routine assessment of renal function (creatinine and/or eGFR) within 6–8 weeks of SGLT-2 initiation since there is likely to be a transient deterioration and this is not a reason to withdraw the drug.
- 14 We recommend that sick day guidance applies, during which SGLT-2 inhibitors should be temporarily withheld.

Areas that require future research

- 1 Research needs to establish whether the cardiovascular and renal benefits of SGLT-2 inhibitors also extend to people with type 2 diabetes who have an eGFR of $<25 \text{ mL/min/1.73 m}^2$, where the glycaemic effect of these drugs is minimal.
- 2 The beneficial renal effects of the SGLT-2 inhibitor class need to be confirmed for people with lesser degrees of albuminuria.
- 3 The long-term impact of SGLT-2 inhibitors on metabolic bone disease, and parameters such as calcium, phosphate and magnesium should be investigated.
- 4 Safety and efficacy of these medications on immunosuppression in people with diabetes who have had a transplant (both pre and post transplant) needs to be assessed.

Audit standards

- 1 The proportion of people with CKD on SGLT-2 inhibitors who have received sick day guidance ([Appendix A](#)).
- 2 The proportion of people in whom SGLT-2 inhibitors were stopped during acute illness, but were not re-initiated on recovery.
- 3 The number of people with CKD stage 3a who are being treated with higher doses of canagliflozin and empagliflozin (currently off-licence).
- 4 The number of people with CKD stage 3b who are being treated with SGLT-2 inhibitors off-licence (dapagliflozin, empagliflozin and ertugliflozin).
- 5 The number of people with CKD on a combination of SGLT-2 inhibitors and GLP-1RAs.

Evidence base

The hypoglycaemic mechanism of action of SGLT-2 inhibitors is to inhibit the reabsorption of glucose that has been filtered by the glomeruli in the kidneys.¹⁹⁴ For this reason, their glucose lowering is limited by declining renal function (since the amount of filtered glucose is reduced). In 2021, there are four SGLT-2 inhibitors licensed in the UK for glucose lowering (dapagliflozin, canagliflozin, empagliflozin and ertugliflozin) and only canagliflozin is currently recommended for initiation when an individual's eGFR is <60 mL/min/1.73 m² (ie CKD stage 3a). Canagliflozin can be initiated down to an eGFR of 45 mL/min/1.73 m² but can only be prescribed at its higher 300 mg dose when the eGFR is ≥ 60 mL/min/1.73 m². In Europe, including the UK, all SGLT-2 inhibitors should be withdrawn when the eGFR falls below 45 mL/min/1.73 m² (ie CKD stage 3b), with the caveat below applying to certain individuals treated with canagliflozin. Dapagliflozin and ertugliflozin doses do not need to be altered according to eGFR, while canagliflozin and empagliflozin should only be used at their lower doses in people with stage 3a CKD.

In 2020, canagliflozin received a licence update for the treatment of diabetic kidney disease as an add-on to standard of care (eg ACE-inhibitors or ARBs) at a dose of 100 mg once daily.¹⁹⁵ The licence allows for initiation of canagliflozin down to an eGFR of 30 mL/min/1.73 m² and continuation for individuals already taking canagliflozin to the point of renal replacement therapy. This change follows similar licence changes in Canada and elsewhere in the world.¹⁹⁶

There was initially a concern that drugs which primarily affect the kidneys (not previously a target organ 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.¹⁹⁷ Post-marketing reports from the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) identified a potential signal for acute kidney injury (AKI) with SGLT-2 inhibitors.¹⁹⁸ This probably reflected the initial decline in eGFR due to the known renal haemodynamic effects of SGLT-2 inhibition.¹⁹⁹ In contrast, three large cardiovascular outcome trials for SGLT-2 inhibitors have shown evidence for renoprotection, and this was also seen in individuals who had an eGFR of 30–60 mL/min/1.73 m², people in whom SGLT-2 inhibitors would currently not be initiated for glucose lowering.^{200,201,202} In addition, the CANVAS²⁰¹, DECLARE-TIMI²⁰² and VERTIS CV²⁰³ trials showed a numerical reduction in acute kidney injury (AKI) in those receiving an SGLT-2 inhibitor versus placebo. These findings are supported by a subsequent systematic review and meta-analysis of three published cardiovascular outcome trials (CVOTs) indicating a lower risk of AKI.²⁰⁴

A meta-analysis of randomised clinical trials has shown that SGLT-2 inhibitors marginally increase serum magnesium levels in people with type 2 diabetes, which appears to be a drug-class effect.²⁰⁵ Further investigations are required to examine the clinical significance of elevated magnesium levels in individuals with type 2 diabetes.

Adverse events

Adverse events which 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 anti-fungal medication, although some people have recurrent episodes that require withdrawal of the SGLT-2 inhibitor.²⁰⁶

Urinary tract infection

While in some studies there has been a significant increase in urinary tract infection (UTI) in people who receive an SGLT-2 inhibitor,²⁰³ this is not a consistent finding and there is still uncertainty about whether this is a true side effect of the drug class.²⁰⁷ An increased risk of urosepsis has not been reported.

Fournier's gangrene (necrotising fasciitis of the perineum and genitalia)

In 2018 the US FDA issued a warning concerning cases of the rare but serious infection of the genitals and surrounding area (termed Fournier's gangrene), in association with SGLT-2 inhibitor use.²⁰⁸ This followed 12 cases which were reported to the FAERS and led to a warning in the summary of product characteristics of all four currently available SGLT-2 inhibitors. An online alert was subsequently posted in the UK.²⁰⁹ People developing this condition should seek urgent medical treatment. It is of note that in the DECLARE-TIMI 58 trial²⁰² there were six cases (out of a total of 17,160 recruits), five of whom received placebo. Also, in a subsequent meta-analysis of 84 trials enrolling 42,415 people treated with an SGLT-2 inhibitor, there was no signal for an increased risk versus comparators (although the number of events was small).²¹⁰

Diabetic ketoacidosis

Warnings about diabetic ketoacidosis (DKA) in people who are receiving SGLT-2 inhibitors have been issued by both the FDA and the European Medicines Agency (EMA).^{211,212} 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).²¹³ Although there was an initial bias towards a diagnosis of 'euglycaemic DKA', other cases appear to be associated with significant hyperglycaemia. Also, some of the reported cases were people with misdiagnosed type 1 diabetes or latent autoimmune diabetes in adult-life (LADA). Other common features were large reductions of insulin dose and established precipitants of DKA, such as starvation, vomiting, dehydration, infection and surgery. Sick day guidance ([Appendix A](#)) and additional user information ([Appendix B](#)) should be recommended for people being treated with SGLT-2 inhibitors, with temporary drug cessation. It is also prudent to withhold SGLT-2 inhibitors in people prior to planned surgical procedures so as to reduce the DKA risk, and in those with anorexia and risk of vomiting, for example during chemotherapy.

There has been a numerical increase in DKA in people receiving a SGLT-2 inhibitor in each of the large CVOTs.^{200–203} and this was statistically significant in both CANVAS²⁰¹ and DECLARE-TIMI 58.²⁰² In the CREDENCE trial³⁹ the numbers of DKA cases were low (11 people receiving canagliflozin versus one receiving a placebo) giving rates of 2.2 versus 0.2 events per 1,000 patient years.

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 2015.²¹⁴ A study subsequently confirmed a reduction in bone mineral density in people who receive canagliflozin, and a meta-analysis reported that fracture risk was increased in canagliflozin-treated individuals.^{215,216} The Canagliflozin Cardiovascular Assessment (CANVAS) study subsequently confirmed a significant increase in fractures in people who received canagliflozin although there was no signal for this adverse event in the CREDENCE trial.^{201,39} This signal has not been

seen with other SGLT-2 inhibitors and so it is currently unknown whether bone fracture is a true safety issue.

Amputation

The FDA issued a warning regarding lower limb amputation (LLA) in 2016, following an interim safety analysis of the CANVAS study of canagliflozin.²¹⁷ 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.²⁰¹ This led to a further FDA safety announcement although, once again, the CREDENCE trial of canagliflozin, which included a population at a high risk for amputation, did not report an adverse signal for this adverse event.²¹⁸ To date, an increased risk of amputation has not been reported in large RCTs of the other SGLT-2 inhibitors. However, a register-based cohort study of new users of SGLT-2 inhibitors in Sweden and Denmark reported an increased risk of lower limb amputation versus GLP-1 receptor agonists (HR 2.32; CI 1.37–3.91).²¹⁹

Empagliflozin

Empagliflozin was the first of the oral hypoglycaemic agents to show superiority over 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 people were randomly assigned to receive empagliflozin 10 mg or 25 mg once daily or placebo, and they remained under observation for a median of 3.1 years.²⁰⁰ The primary outcome of death from cardiovascular causes, non-fatal myocardial infarction (MI) and non-fatal stroke (three-point major adverse cardiac events (MACE) endpoint) occurred in 490 out of 4,687 people (10.5%) in the pooled empagliflozin group and in 282 out of 2,333 people (12.1%) in the placebo group. This gave a HR in the empagliflozin group of 0.86 (95% 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 people 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 participants in this cohort). Trial participants 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 people with the highest risk of cardiovascular events gain a benefit in MACE reduction from SGLT-2 inhibition.

Pre-specified secondary analyses of renal outcomes from the EMPA-REG OUTCOME trial have subsequently been published.²²⁰ 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)²²⁰ and all of the individual renal outcomes were reduced in

the empagliflozin groups. Follow-up analyses indicate that these benefits are seen in Asian people²²¹ and were independent of HbA1c lowering.²²²

In a subsequent exploratory, non-prespecified analysis of EMPA-REG OUTCOME the influence of baseline background medications which also alter intra-renal haemodynamics was investigated.²²³ The medications assessed were angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, diuretics and non-steroidal anti-inflammatory drugs, all of which are commonly prescribed in type 2 diabetes mellitus. The authors reported that reductions in renal outcome with empagliflozin were consistent across medication subgroups with no heterogeneity seen, implying benefit irrespective of baseline medication. A similar analysis investigated whether progression of CKD in the EMPA-REG OUTCOME trial was affected by baseline glucose-lowering therapy.²²⁴ Empagliflozin was found to reduce incident or worsening nephropathy versus placebo, which was irrespective of baseline SU or insulin use. However, there was a greater reduction in this risk for people who were not taking metformin at baseline (HR 0.47; 95% CI 0.37–0.59) versus those who were (HR 0.68; 95% CI 0.58–0.79; p-interaction=0.01). The authors suggested a larger benefit from empagliflozin in this cohort although the finding could be due to confounding variables, for example, people not taking metformin are those at higher risk due to comorbidities (age, eGFR etc).

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.²²⁵ 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 people with normoalbuminuria; –25% (–31 to –19; p<0.0001) in people with microalbuminuria; and –32% (–41 to –23; p<0.0001) in people with macroalbuminuria. These reductions were maintained at 164 weeks and remained significant after cessation of treatment for those with baseline microalbuminuria and macroalbuminuria. People who received empagliflozin were also more likely to experience a sustained improvement from microalbuminuria to normoalbuminuria (HR 1.43; 95% CI 1.22–1.67; p<0.0001) and from macroalbuminuria to microalbuminuria or normoalbuminuria (HR 1.82; CI 1.40–2.37; p<0.0001). The EMPA-REG OUTCOME study showed that in terms of albumin excretion, the absolute benefit was greatest in those with raised UACR.

Other post hoc analyses of the EMPA-REG OUTCOME trial have investigated the impact of baseline kidney disease on renal outcomes. In one, the trial recruits were grouped according to KDIGO (Kidney Disease Improving Global Outcomes) risk categories; patients were assigned according to eGFR and UACR as low (47% of total), moderately increased (29%), high (15%) and very high (8%) risk.²²⁶ Empagliflozin showed consistent reductions in various kidney outcomes across the four categories. In a subsequent analysis, participants were grouped as follows: overt diabetic kidney disease (DKD) – defined as UACR >33.9 mg/mmol (>300 mg/g) irrespective of eGFR; non-overt DKD – eGFR <60 mL/min/1.73 m² or UACR ≤33.9 mg/mmol (≤300 mg/g); and ‘all others’ – eGFR ≥60 mL/min/1.73 m² and UACR ≤33.9 mg/mmol (≤300 mg/g).²²⁷ Empagliflozin improved kidney outcomes in patients with DKD irrespective of the albuminuria status. These analyses indicate that the beneficial effect of empagliflozin in EMPA-REG OUTCOME on the relative risk of CV and renal outcomes was seen irrespective of baseline renal status. However, those with elevated levels of albuminuria were at greatest risk of CV and renal deterioration and gained the greatest absolute benefit in terms of their reduction; this highlights the importance of UACR in targeting patients who will gain most from treatment with empagliflozin.

The EMPEROR-reduced trial was a double-blind trial of empagliflozin 10 mg once daily versus placebo, in addition to recommended therapy, in patients with chronic heart failure stages II–IV with a reduced left ventricular ejection fraction (≤40%) and elevated NT-proBNP (N-

terminal of the prohormone brain natriuretic peptide).²²⁸ Of the 3,730 individuals recruited, 50% had type diabetes and the renal exclusion criteria were eGFR <20 mL/min/1.73 m² or dialysis. Pre-specified secondary renal endpoints included eGFR slope change from baseline and a composite of time to first occurrence of chronic dialysis, renal transplant or sustained reduction of eGFR. The decline in eGFR was significantly less in the empagliflozin group (–0.55 mL/min/1.73 m² per year versus –2.28 mL/min/1.73 m² for placebo) (p<0.001). The composite renal outcome occurred in 30 patients who received empagliflozin (1.6%) and in 58 placebo patients (3.1%) (HR 0.50; 95% CI 0.32–0.77). The authors concluded that the ability of empagliflozin to preserve renal function in people with type 2 diabetes is also seen in those with co-existing heart failure. A subsequent analysis showed that baseline HbA1c (both in and outwith the diabetes range) assessed as a continuous variable did not significantly modify the beneficial impact of empagliflozin on renal outcomes.²²⁹

Another pre-specified analysis of the EMPEROR-Reduced trial examined the impact of baseline CKD on a composite kidney outcome of sustained profound fall in eGFR, chronic dialysis or renal transplant.²³⁰ Baseline CKD was defined as eGFR <60 mL/min/1.73 m² or UACR 33.9 mg/mmol (>300 mg/g) and the renal outcomes were as specified for the main trial. Empagliflozin slowed the slope of eGFR decline by 1.11 (0.23–1.98) mL/min/1.73 m²/year in people with CKD and by 2.41 (1.49–3.32) mL/min/1.73 m²/year in those without. The occurrence of the composite kidney outcome was similarly reduced in both cohorts. The effect of empagliflozin was consistent across a wide range of baseline kidney measures, including individuals with an eGFR as low as 20 mL/min/1.73 m².

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).²³¹ Overall, the incidence of renal adverse events was low and similar in canagliflozin and non-canagliflozin treated groups. In a study versus glimepiride,²³² 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*²³³ performed a secondary analysis of the same clinical trial of people who were randomly assigned to either canagliflozin 100 mg once daily, canagliflozin 300 mg once daily or glimepiride up-titrated to 6–8 mg once daily.²³² The endpoints were annual change in albuminuria and eGFR over 2 years 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 people with a baseline UACR of >3.39 mg/mmol (>30 mg/g), UACR 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 implied 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 high cardiovascular risk.²⁰¹ 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 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 for 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; need for renal-replacement therapy; or death from renal causes (HR 0.60; 95% CI 0.47–0.77).

The CREDENCE study³⁹ was the first study of an SGLT-2 inhibitor to have renal outcomes in its primary composite endpoint. People with type 2 diabetes and albuminuric chronic kidney disease were randomised to receive canagliflozin 100 mg once daily or placebo. All participants had an eGFR of 30 to < 90 mL/min/1.73 m², albuminuria (albumin:creatinine ratio > 33.9 –565 mg/mmol (> 300 to 5,000 mg/g) and received renin-angiotensin system blockade. Sixty per cent of recruits had an eGFR of 30–60 mL/min/1.73 m². The primary endpoint was a composite of end-stage kidney disease (dialysis, transplantation, or sustained eGFR of < 15 mL/min/1.73 m²), a doubling of the serum creatinine or death from renal or cardiovascular causes.

The trial was halted early after a planned interim analysis, at which point 4,401 people had been randomised with median follow-up of 2.6 years. The relative risk of the primary endpoint was significantly lower in the canagliflozin group with event rates of 43.2 versus 61.2 per 1,000 patient-years (HR 0.70; 95% CI 0.59–0.82; $p = 0.00001$). The relative risk of the renal-specific composite of end-stage kidney disease, doubling of the creatinine level, or death from renal causes was lower by 34% (HR 0.66; 95% CI 0.53–0.81; $p < 0.001$) and end-stage kidney disease was lower by 32% (HR 0.68; 95% CI 0.54–0.86; $p = 0.002$). Participants in the canagliflozin group also had a significantly lower risk of cardiovascular death, myocardial infarction, or stroke (HR 0.80; 95% CI 0.67–0.95; $p = 0.01$) and hospitalisation for heart failure (HR 0.61; 95% CI 0.47–0.80; $p < 0.001$). Of note, in this high-risk population there were no significant increases in rates of lower limb amputation or fracture.

A subsequent analysis of CREDENCE²³⁴ assessed the impact of canagliflozin on people with and without cardiovascular disease at baseline. The latter cohort were classified as ‘primary prevention’ although the presence of albuminuria would still leave them at significant cardiovascular and renal risk. A total of 2,181 (49.6%) participants had no history of documented cardiovascular disease and were younger (61.4 vs 64.6 years), more often female (36.6% vs 31.3%), and Asian (24.4% vs 15.5%), with a shorter duration of diabetes (15.2 vs 16.4 years) compared with ‘secondary prevention’ participants. Both groups had similar mean eGFR (56.8 vs 55.5 mL/min/1.73 m²) and median UACR (106.6 vs 105 mg/mmol [943 vs 903 mg/g]).

Canagliflozin reduced the risk of major cardiovascular events in both the primary (HR 0.68; 95% CI 0.49–0.94) and secondary (HR 0.85; 95% CI 0.69–1.06) prevention groups (p -interaction 0.25). This is noteworthy since a meta-analysis of SGLT-2 inhibitor CVOTs had shown no CV benefit in people without known atherosclerotic CVD.²³⁵ The risk of the primary composite renal outcome and the composite of cardiovascular death or hospitalisation for heart failure were also consistently reduced in both primary and secondary prevention cohorts (p -interaction > 0.5 for each outcome). These data indicate that canagliflozin provides benefit in albuminuric type 2 diabetes, irrespective of existing cardiovascular disease.

Cannon *et al* performed an additional analysis of the CREDENCE data which found that canagliflozin reduced the risk of both CV and renal events without a significant interaction across the spectrum of baseline HbA1c values and this included people with baseline HbA1c between 48–53 mmol/mol (6.5% and 7%).²³⁶ This strongly suggests that treatment of people

with CKD and/or ASCVD with a SGLT-2 inhibitor is warranted, even if their diabetes is 'well controlled' and supports the concept that SGLT-2 inhibitors have clinical benefits regardless of HbA1c.

A secondary analysis of CREDENCE used Cox proportional hazards regression to assess the effects on renal efficacy and safety outcomes in baseline eGFR subgroups 30–45, 45–60 and 60–90 mL/min/1.73 m² and linear mixed effects models to analyse the effects on eGFR slope.²³⁷ Subgroups with lower eGFRs showed larger absolute benefits for renal outcomes but the relative benefits of canagliflozin for renal outcomes were consistent across eGFR subgroups (all p-interaction >0.11). Serious adverse events, including amputations and fractures, were consistent across eGFR subgroups with no increases attributable to canagliflozin. In all subgroups, canagliflozin led to an acute drop in eGFR which was followed by stabilization in eGFR decline.

Another *post-hoc* analysis of CREDENCE assessed the relationship between reduction in albuminuria in the first 26 weeks of study and renal outcomes (end-stage kidney disease, doubling of serum creatinine or kidney death).²³⁸ Canagliflozin lowered UACR by 31% (95% CI 27–36%) at week 26 and increased the likelihood of achieving a 30% reduction in UACR (OR 2.69, 95% CI 2.35–3.07). In continuous analyses, each 30% decrease in UACR over the first 26 weeks was independently associated with a lower hazard for kidney outcomes (HR 0.71, 95% CI 0.67–0.76, p<0.001).

Dapagliflozin

Twelve double-blind, placebo-controlled, randomised clinical trials that included 4,545 participants were analysed up to 24 weeks.²³⁹ Six of the studies also included longer-term data (up to 102 weeks [n=3,036 participants]). People 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 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 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 people with renal adverse events up to 24 weeks and, in this subgroup only, renal adverse events were more common in dapagliflozin-treated people than those in the placebo group, but with no dose dependence.

One publication and several abstracts reported on the effect of dapagliflozin on the surrogate renal endpoint of change in UACR.²⁴⁰ These were post-hoc analyses of pooled data from phase III clinical trials which showed a reduction in albuminuria that appeared to be independent of changes in HbA1c, blood pressure (BP), body weight and eGFR.

The DELIGHT (albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycaemic control in people with type 2 diabetes and chronic kidney disease trial)²⁴¹ was a double-blind, placebo-controlled trial which enrolled 461 people. A total of 145 people were randomly assigned to the dapagliflozin group, 155 to the dapagliflozin–saxagliptin group and 148 to the placebo group. People with type 2 diabetes had UACR of 3.39–395.5 mg/mmol (30–3,500 mg/g), an eGFR of

25–75 mL/min/1.73 m² and were receiving stable doses of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker therapy and glucose-lowering treatment for at least 12 weeks.

Primary endpoints at 24 weeks were change from baseline UACR (dapagliflozin and dapagliflozin–saxagliptin groups) and HbA1c (dapagliflozin–saxagliptin group). Dapagliflozin and dapagliflozin–saxagliptin reduced UACR versus placebo (mean UACR change from baseline was –21.0% (95% CI –34.1 to –5.2; $p=0.011$) for dapagliflozin and –38.0% (–48.2 to –25.8; $p<0.0001$) for dapagliflozin–saxagliptin. Minimal and non-significant eGFR reductions were seen in both the dapagliflozin and dapagliflozin–saxagliptin groups (mean change from baseline of –2.4 mL/min/1.73 m² (–4.2 to –0.5; $p=0.011$) in the dapagliflozin group and –2.4 mL/min/1.73 m² (–4.2 to –0.7; $p=0.0075$) in the dapagliflozin–saxagliptin group versus placebo). This reduction was completely reversible after treatment discontinuation. There were no new drug-related safety issues. The DELIGHT trial thus showed that dapagliflozin with or without saxagliptin (given in addition to conventional treatments), reduced proteinuria and slowed the progression of kidney disease in people with type 2 diabetes and moderate-to-severe chronic kidney disease.

The DECLARE-TIMI 58 study²⁰² was the cardiovascular outcomes trial for dapagliflozin versus placebo. The primary safety outcome was a composite of MACE (cardiovascular death, myocardial infarction, or ischemic stroke) but there were two co-primary efficacy outcomes; the same three component MACE and a composite of cardiovascular death or hospitalization for heart failure. A renal composite ($\geq 40\%$ decrease in eGFR to <60 mL per minute, new end-stage kidney disease, or death from renal or cardiovascular causes) was a key secondary endpoint, as was death from any cause. 17,160 people, including 10,186 (59%) without atherosclerotic cardiovascular disease, were followed for a median of 4.2 years.

Dapagliflozin met the prespecified criterion for noninferiority regarding safety for MACE (upper boundary of the 95% CI <1.3 ; $p<0.001$) but did not result in a significantly lower rate of MACE (8.8% versus 9.4% in the placebo group; HR 0.93; 95% CI 0.84–1.03; $p=0.17$). However, there was a significantly lower rate of cardiovascular death or hospitalisation for heart failure (4.9% vs. 5.8%; HR 0.83; 95% CI 0.73–0.95; $p=0.005$), driven by the lower rate of hospitalisation for heart failure (HR 0.73; 95% CI 0.61–0.88). Renal events were recorded in 4.3% dapagliflozin-treated subjects versus 5.6% in the placebo group (HR 0.76; 95% CI 0.67–0.87).

A more detailed renal analysis of DECLARE-TIMI 58 was subsequently published.²⁴² At baseline, 8,162 individuals (48%) had an eGFR ≥ 90 mL/min/1.73 m², 7,732 (45%) 60–89 mL/min/1.73 m² and 1,265 (7%) eGFR less than 60 mL/min/1.73 m². The HR for the renal-specific outcome was 0.53 (0.43–0.66; $p<0.0001$) with a 46% reduction in sustained decline in eGFR by at least 40% to less than 60 mL/min/1.73 m² (1.4% versus 2.6%; HR 0.54; 95% CI 0.43–0.67; $p<0.0001$). The risk of end-stage kidney disease or renal death was also significantly lower in the dapagliflozin group (0.1% versus 0.3%; HR 0.41; 95% CI 0.20–0.82; $p=0.012$). The improvements in cardiorenal and renal-specific composite outcomes were seen across prespecified subgroups defined according to baseline eGFR and atherosclerotic cardiovascular disease status with no evidence of statistical interaction. Regarding changes in eGFR, the mean decrease was larger in the dapagliflozin group 6 months after randomisation, equalised by 2 years, and then at 3 and 4 years the mean decrease was less with dapagliflozin than with placebo. Of note, these outcomes were seen in people with type 2 diabetes both with and without established atherosclerotic cardiovascular disease and on a background of preserved renal function (mean baseline eGFR 85 mL [±16]/min/1.73 m²). A subsequent analysis of DECLARE-TIMI 58 according to age at baseline showed that the renal-specific composite outcome was reduced with dapagliflozin in all three age-groups (<65 , 65–75 and >75 years) with no age-based treatment interactions.²⁴³

The Dapagliflozin and Prevention of Adverse-outcomes in Heart Failure trial (DAPA-HF) was a multicentre, parallel group, randomized, double-blind, study in people with chronic heart failure, which evaluated the effect of dapagliflozin 10 mg once daily versus placebo, in addition to standard care. The primary composite outcome was a worsening heart failure event (hospitalisation or urgent heart failure visit) or cardiovascular death. Patients both with and without diabetes were eligible with left ventricular ejection fraction $\leq 40\%$, moderately elevated N-terminal pro B-type natriuretic peptide level and an eGFR ≥ 30 mL/min/1.73 m².²⁴⁴ A total of 4,744 participants were randomised, of whom 42% had type 2 diabetes.²⁴⁵ The primary composite outcome occurred in 386 participants (16.3%) in the dapagliflozin group and in 502 (21.2%) in the placebo group (hazard ratio, 0.74; 95% CI, 0.65 to 0.85; $p < 0.001$). Event rates for all three components of the composite outcome favoured dapagliflozin and the number needed to treat to prevent one primary event was 21 (95% CI, 15 to 38). The impact of dapagliflozin on the primary composite was unaffected by baseline eGFR (< 60 versus ≥ 60 mL/min/1.73 m²). The incidence of a pre-specified renal composite outcome did not differ between the treatment groups.

The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial assessed the effect of dapagliflozin on renal and cardiovascular events in people with CKD (both with and without diabetes).²⁴⁶ 4,094 participants with an eGFR between 25–75 mL/min/1.73 m² and UACR of 22.6–565 mg/mmol (200–5,000 mg/g) were randomised to receive dapagliflozin 10mg once daily or placebo. Participants were on stable dose of ACEi or ARB although those who were unable to take these medications could be included. The primary outcome was a composite of sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes.

The trial was stopped early because of efficacy.²⁴⁷ Over a median of 2.4 years, the primary outcome event occurred in 197 of 2,152 participants (9.2%) in the dapagliflozin group and 312 of 2,152 participants (14.5%) in the placebo group (HR 0.61; 95% CI 0.51 to 0.72; $p < 0.001$) and the number needed to treat to prevent one primary outcome event was 19 [95% CI, 15–27]). The hazard ratio for the renal composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes was 0.56 (95% CI 0.45 to 0.68; $p < 0.001$). All-cause mortality was 101 dapagliflozin participants (4.7%) versus 146 subjects (6.8%) in the placebo group (HR 0.69; 95% CI 0.53 to 0.88; $p = 0.004$). The effects were similar in people with type 2 diabetes (67.5%) versus those without. The mean baseline eGFR was 41.1 mL/min/1.73 m² and the median UACR was 107.2 mg/mmol (949 mg/g); the primary endpoint reduction for dapagliflozin was similar according to baseline eGFR (< 45 versus ≥ 45 mL/min/1.73 m²) and UACR ≤ 113 vs > 113 mg/mmol ($\leq 1,000$ vs $> 1,000$ mg/g).

Ertugliflozin

Ertugliflozin was studied in a phase 3 trial which included 468 people with type 2 diabetes and stable stage 3 CKD (eGFR 30–59 mL/min/1.73 m²) treated over 52 weeks.²⁴⁸ The primary endpoint was change in HbA1c but the study also assessed safety outcomes, as well as changes in eGFR and UACR. Renal-related AEs (defined according to a standard MedDRA composite renal query) were similar in the placebo and ertugliflozin groups and there was no difference in adverse hyperkalaemia events. Modest reductions in mean eGFR were observed in the ertugliflozin groups after 6 weeks followed by a slight increase toward baseline. At week 52, a similar proportion of people in each treatment arm had changed from normoalbuminuria to microalbuminuria.

The effect of ertugliflozin on eGFR and UACR was also assessed over 104 weeks using pooled data from two randomised controlled, active comparator trials from the eValuation of ERTugliflozin efficacy and Safety (VERTIS) programme.²⁴⁹ In the VERTIS SU study, ertugliflozin

was compared with glimepiride while in the VERTIS MET study, ertugliflozin was compared versus placebo until 26 weeks and then to blinded glimepiride for the remainder of the study. The mean baseline eGFR was 88.2 mL/min/1.73 m² and geometric mean of baseline UACR was 1.31 mg/mmol (11.6 mg/g). At 104 weeks the changes in eGFR were -0.2, 0.1 and -2.0 mL/min/1.73 m² for the ertugliflozin 5 mg, ertugliflozin 15 mg and non-ertugliflozin groups. Among those subjects with raised UACR at baseline, the ertugliflozin groups had greater reductions in UACR; at week 104, the corrected difference in UACR was -29.5% (p<0.01) for ertugliflozin 5 mg once daily and -37.6% (p< 0.001) for ertugliflozin 15 mg once daily.

The VERTIS CV trial was the CVOT for ertugliflozin²⁵⁰ and this included 8,246 people with type 2 diabetes, established atherosclerotic cardiovascular disease and eGFR >30 mL/min/1.73 m².²⁰³ Following protocol revision, the trial also included an efficacy assessment for a renal composite outcome made up of renal death, dialysis/transplant or doubling of serum creatinine. At baseline, the mean eGFR of the study population was 76 mL/min/1.73 m², microalbuminuria was present in 30.2% and macroalbuminuria (>33.9 mg/mmol [>300 mg/g]) in 9.2%. VERTIS CV was an event-driven study with a primary composite endpoint of MACE (CV death, nonfatal MI, nonfatal stroke) for non-inferiority. Secondary endpoints for superiority were: a composite outcome of CV death and hospitalisation for heart failure (HHF); CV death; and the renal composite. There was a hierarchical testing sequence across the primary and key secondary superiority outcomes. Trial recruits were allocated to placebo (2,747) or two doses of ertugliflozin, 5 mg (n=2,752) and 15 mg (n=2,747). 87.4% of subjects completed the study and vital status was available for over 99%, however, premature discontinuation of the study medication occurred in 27.9% of the placebo group and 23.5% of patients receiving ertugliflozin.

The median duration of follow-up was 3.5 years and the primary composite MACE outcome was seen in 11.9% of the combined ertugliflozin groups and 11.9% of the placebo cohort (HR 0.97; CI 0.85–1.11) confirming non-inferiority (p<0.001) but not superiority. The secondary composite endpoint of CV death or HHF showed a trend in favour of ertugliflozin (HR 0.88; CI 0.75–1.03) but, once again, this was non-significant (p=0.11), thus ending the hierarchical significance testing. The analysis of HHF showed numerical benefit for ertugliflozin (HR 0.70; CI 0.54–0.90), indicating a 30% reduction with confidence intervals less than unity, and so was consistent with the CVOTs of the other three licensed SGLT-2 inhibitors. However, the renal composite (which was very similar to the 'hard renal outcomes' assessed in EMPA-REG OUTCOME) was not significantly reduced by ertugliflozin (HR 0.81; CI 0.63–1.04, p=0.08) although the eGFR slopes over time looked similar to those reported for other SGLT-2 inhibitors (consistent with renal protection).

Overall, the results from the VERTIS CV study were a little disappointing, especially given that all of the trial recruits were at particularly high CV risk, having previously experienced an atherosclerotic cardiovascular event. Subsequent in-depth analyses and comparisons with the other SGLT-2 inhibitor CVOTs may point to reasons for what initial meta-analyses suggest may be heterogeneity within the class.²⁰³

A pre-specified exploratory analysis of VERTIS CV assessed the impact of ertugliflozin on CV events according to baseline renal function (eGFR, CKD stage, UACR and KDIGO risk category).²⁵¹ Twenty-five per cent of patients had CKD stage 1, 53% CKD stage 2, and 22% CKD stage 3: 60% of subjects had normal and 40% elevated albuminuria. Regarding KDIGO CKD risk categories, 49%, 32%, and 19% were classified as low-, moderate-, and high-/very high-risk. Event rates were higher for all reported CV outcomes with more advanced kidney disease. Risk reductions with ertugliflozin achieved significance for HHF and the composite of HHF/CV death in the CKD stage 3 subgroup, in patients with elevated albuminuria, and the

KDIGO CKD moderate- and high-/very high-risk categories; the highest absolute event rate reductions were also greatest in these subgroups.

Current position

The cardiovascular and renal benefits seen with empagliflozin in the EMPA-REG OUTCOME study were unexpected, so replication of these results for canagliflozin was very encouraging for the SGLT-2 inhibitor class. The DECLARE-TIMI 58 CVOT for dapagliflozin did not show superiority for the 3-point MACE co-primary outcome but the population studied was a lower risk cohort. A meta-analysis of these three SGLT-2 inhibitor CVOTs²⁴² also suggested no heterogeneity and there is supportive evidence of cardiovascular benefit for dapagliflozin from real-world database analyses.^{252,253} As a result, guidelines for the management of type 2 diabetes have been updated in Europe and elsewhere with SGLT-2 inhibitors regarded as second-line therapy, irrespective of glycaemic control,^{254,255} or even first-line drugs²⁵⁶ for people with type 2 diabetes and established CVD.^{257,258} The results of the VERTIS CV trial did not confirm cardiovascular benefit for ertugliflozin and the renal data were less impressive; at least the positive impact on hospitalisation for heart failure was consistent with a class effect.

The CREDENCE study has led to a change in licence for canagliflozin in the EU and the DAPA-CKD study of dapagliflozin is entirely consistent with a reno-protective class effect.²⁴⁷ Data for empagliflozin²⁵⁹ will provide additional data on primary renal outcomes. For now, systematic reviews and meta-analyses^{204,260} suggest a clear beneficial class effect on the risk of dialysis, transplantation and death due to kidney disease. These effects are seen irrespective of baseline albuminuria (implying prevention) and use of renin angiotensin system blockade. The absolute risks and absolute benefits are greatest in people with albuminuric DKD; the cardiorenal outcomes are independent of blood glucose-lowering effects and use of RAAS blockade or diuretics.

Practical aspects

Based on the above clinical trial data, we recommend the initiation of canagliflozin in people with type 2 diabetes and albuminuria (UACR >33.9 to 565 mg/mmol [>300 to $5,000$ mg/g]) down to an eGFR of $30 \text{ mL/min/1.73 m}^2$. Regardless of UACR, we also recommend the initiation of dapagliflozin as licensed for people with heart failure and CKD where eGFR is $>30 \text{ mL/min/1.73 m}^2$. It is likely that all SGLT-2 inhibitors will be effective in these individuals but licence updates are awaited. We caution against use of SGLT-2 inhibitors in people with a current or previous medical history of foot ulceration and DKA. We do not recommend routine checking of renal function within 6–8 weeks of SGLT-2 inhibitor initiation, since the anticipated fall in eGFR is transient and should not lead to therapy cessation. We strongly suggest that SGLT-2 inhibitors should be withheld during acute illness, at which point plasma glucose and ketones should be assessed. We also recommend treatment suspension prior to surgery or other procedures requiring prolonged fasting.

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 people 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 people 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 evidence of protection from cardiovascular disease with some GLP-1RAs in people 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 people with stage 3 CKD; GLP-1RAs are, therefore, preferred over alternative glucose-lowering therapies (eg sulfonylureas and insulins) in this scenario (Grade 2B).
- 3 There is no conclusive 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 people with stage 1–2 CKD; however, we only recommend the use of drugs that have a licensed indication for CKD stages 3 and 4 (Grades 1A–1C). No GLP-1RAs are currently licensed for use in people with CKD stage 5 in the UK, nor for those on renal dialysis.
- 4 People 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 drugs that can cause hypoglycaemia (such as sulfonylureas and insulins) (Grade 1A).
- 5 There is no role for the combination of GLP-1 analogues and DPP-4 inhibitors (Grade 1C).

Areas that require future research

- 1 There is a need for studies on GLP-1RAs that have hard renal endpoints as their primary outcome (published 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 people with stage 5 CKD, including those who are on renal dialysis (both haemodialysis and continuous peritoneal dialysis) and those who have undergone renal transplantation.
- 3 Studies of GLP-1RAs are needed in people with type 2 diabetes following renal transplantation.
- 4 There is a need to examine the risk of worsening diabetic retinopathy in people with type 2 diabetes and CKD treated with GLP-1RAs, in light of the fact that three studies have shown a signal for deterioration (one significant) despite improving proteinuria endpoints.
- 5 The use of a combination of GLP-1RAs and SGLT-2 inhibitors needs to be examined in people with CKD, with a focus on renal endpoints.
- 6 The use of a combination of GLP-1RAs and insulin needs to be examined in people with CKD, with a focus on renal endpoints.

Audit standards

- 1 The proportion of people with CKD on GLP-1RAs who have received sick day guidance ([Appendix A](#)).
- 2 The proportion of people in whom GLP-1RAs were stopped during acute illness, but were not re-initiated on recovery.
- 3 The frequency of off-licence use of GLP-1RAs in people with CKD stage 4 (exenatide and lixisenatide) and stage 5 (liraglutide, dulaglutide and semaglutide).
- 4 The combination of GLP-1RA and insulin use in people with CKD.
- 5 The combination of GLP-1RA and SGLT-2 inhibitor use in people with CKD.

Evidence base

In 2021, six licensed GLP-1RA injectables are available for use in Europe. A further one (albiglutide), never launched in the UK was globally withdrawn in 2018, and two involve differing delivery mechanisms for the same molecule (exenatide). All had licence limitations based on the presence of CKD, although these limitations have become more relaxed as additional post-marketing studies are performed.

There have been isolated case reports of acute kidney injury (AKI)^{261,262} and interstitial nephritis^{263,264} resulting from exenatide and liraglutide use, and these are referred to in their summary of product characteristics (SPC).^{265,266} Acute hypovolaemia from severe gastrointestinal side effects was considered to be a more likely cause of AKI than a direct nephrotoxic effect of these drugs. In practice, it would be reasonable to apply caution for people who have CKD and acute illness via the temporary cessation of GLP-1RA therapy through general sick day guidance ([Appendix A](#)).

Exenatide

Exenatide is mainly eliminated by the kidneys and its clearance is reduced by 13%, 36% and 84% in mild, moderate and severe kidney 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 kidney disease (ESKD).²⁶⁷

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 required haemodialysis. Some of these occurred in people 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. Reversibility of altered renal function has been described with supportive treatment and discontinuation of exenatide.

In people who are receiving exenatide as twice daily BYETTATM, no dosage adjustment is necessary if they have mild renal impairment (defined as creatinine clearance (CrCl) of 50–80 mL/min). In people 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 people with ESKD who are receiving dialysis, a single 5 mcg dose of BYETTATM increased the frequency and severity of gastrointestinal adverse reactions. BYETTATM is not recommended for use in people with ESKD or severe renal impairment (CrCl of <30 mL/min).

For once-weekly exenatide (Bydureon™), the SPC often refers to BYETTA™ data.²⁶⁸ No dose adjustment of Bydureon™ is necessary for people with mild renal impairment (CrCl of 50–80 mL/min) but clinical experience in people with moderate renal impairment (CrCl of 30–50 mL/min) is very limited, and so Bydureon™ is not recommended for these individuals. It is also not recommended for people who have severe renal impairment (CrCl <30 mL/min) or ESKF.

Liraglutide

Liraglutide is a once-daily GLP-1RA that is metabolised through proteolytic mechanisms and is not predominantly eliminated by a single organ.²⁶⁹ Signs and symptoms of dehydration, including renal impairment and acute renal failure, have been reported in people treated with liraglutide. People who are prescribed liraglutide should be advised about the potential risk of dehydration in relation to gastrointestinal side effects, and should take precautions to avoid fluid depletion.²⁶⁶

A single-dose (0.75 mg subcutaneously) pharmacokinetic trial with liraglutide provided initial evidence that exposure was not increased in people with renal impairment.²⁷⁰ Thirty participants 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), and ESKD requiring dialysis.

The ESKD group only included subjects who were on continuous ambulatory peritoneal dialysis (CAPD) which was continued during the sampling period. 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% CI 0.58–1.34), which was not significant.

Idorn *et al*²⁷¹ reported on 24 people with type 2 diabetes and ESKD who were randomly allocated to 12 weeks of double-blind liraglutide (titrated to a maximum dose of 1.8 mg once daily) or 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 people completed the study period, and dose-corrected plasma trough liraglutide concentration was increased by 49% (95% CI 6–109; $p=0.02$) in the group with ESKD, 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 individuals with ESKD, compared with controls ($p<0.04$). The authors suggested that a reduction in treatment doses and a prolonged titration period may be advisable for people with ESKD.

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 people with mild renal impairment (eGFR of 60 to ≤ 89 mL/min/1.73 m²) was similar to that in people with normal renal function.²⁷² Data from people 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 people who were administered liraglutide once daily (1.2 mg or 1.8 mg) or a placebo as either monotherapy or in combination with oral glucose-lowering therapies 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 people 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 people with moderate or severe renal impairment who were receiving liraglutide, although the number of people 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 2016.²⁷³ A total of 9,340 people with type 2 diabetes were randomised, with 4,668 people being assigned to receive liraglutide and 4,672 people assigned to placebo. In total, 96.8% of the participants 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 people 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 participants did not receive study medication. Overall, 2,158 (23.1%) of the LEADER participants 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 people 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 people with stage 3 CKD or higher 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/1.73 m²), need for continuous renal replacement therapy, and 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.²⁷⁴

The LIRA-RENAL trial was conducted to establish the efficacy and safety of liraglutide as an add-on therapy in people with inadequately controlled type 2 diabetes and moderate renal impairment.²⁷⁵ In total, 279 people with an HbA1c of 53–84 mmol/mol (7–10%), a BMI of 20–45 kg/m², an eGFR of 30–59 mL/min/1.73 m² (calculated by the modification of diet in renal disease (MDRD) equation) were randomised to 1.8 mg liraglutide once daily or 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 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 people 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 people with severe renal impairment (eGFR <30 mL/min/1.73 m²), of whom 117 were randomised to receive liraglutide.^{273,274} As a result of this, the SPC for the EU was updated in 2017 to state the following: 'No dose adjustment is required for people with mild, moderate or severe renal impairment' ie liraglutide can be used in people with an eGFR of >15 mL/min/1.73 m². There is little therapeutic experience in people with ESKD, 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 people with mild and moderate renal impairment confirmed that a 1.2 mg once daily 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.²⁷⁶

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.

The CVOT for lixisenatide²⁷⁷ was a randomised, double-blind, trial comparing once-daily lixisenatide (10–20 µg) with volume-matched placebo in 6,068 participants (ELIXA). ELIXA demonstrated cardiovascular safety, but not superiority, of lixisenatide in people who had experienced a recent acute coronary syndrome (within 180 days of randomisation). An exploratory analysis of ELIXA²⁷⁸ was subsequently performed to investigate the effect of lixisenatide on renal endpoints. The authors reported the change in UACR and eGFR according to prespecified baseline albuminuria (normoalbuminuria [UACR <3.39 mg/mmol {<30 mg/g}]; microalbuminuria [\geq 3.39 to <33.9 mg/mmol { \geq 30 to <300 mg/g}]; and macroalbuminuria [\geq 33.9 mg/mmol {>300 mg/g}]). After 108 weeks, the placebo-adjusted mean percentage change in UACR with lixisenatide was -1.69% (95% CI -11.69 to 8.30; p=0.7398) in people with normoalbuminuria, -21.10% (-42.25 to 0.04; p=0.0502) in people with microalbuminuria, and -39.18% (-68.53 to -9.84; p=0.0070) in people with macroalbuminuria. Lixisenatide was associated with a reduced risk of new-onset macroalbuminuria compared with placebo when adjusted for baseline HbA1c (HR 0.81; 95% CI 0.66–0.99; p=0.04). At the end of the trial, the largest eGFR decline was seen in the macroalbuminuric group, but no significant differences were observed between the two treatment groups. No significant differences in eGFR decline were identified between treatment groups in any UACR subgroup. In the trial safety population, doubling of serum creatinine occurred in 35 (1%) of 3,032 people in the placebo group and 41 (1%) of 3,031 people in the lixisenatide group (HR 1.16; 95% CI 0.74–1.83; p=0.51). The proportion of participants with renal adverse events was low (1.6% in both treatment groups).

No dose adjustment is required for people 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 people during clinical trials.²⁷⁹ There is limited therapeutic experience in people 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.

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

Dulaglutide

Dulaglutide is a once weekly GLP-1RA for glucose lowering that was initially licensed in 0.75 mg and 1.5 mg doses via a disposable injection device.²⁸⁰ 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 people with mild to severe renal impairment (CrCl of <30 mL/min), including those with ESRF (requiring dialysis).²⁸¹ In clinical studies, the dulaglutide safety profile in people with moderate renal impairment was similar to the profile in the overall type 2 diabetes population. These studies did not include people with severe renal impairment or ESKD. A 26-week study comparing dulaglutide with insulin glargine in participants with type 2 diabetes and moderate or severe CKD (AWARD-7) reported comparable glycaemic control.²⁸² 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 UACR exceeded 3.39 mg/mmol (30 mg/g).²⁸³

The CVOT for dulaglutide^{284,285} was a randomised double-blind, placebo-controlled trial which recruited people aged ≥50 years with type 2 diabetes with either a previous cardiovascular event or cardiovascular risk factors. They were assigned weekly subcutaneous injection of dulaglutide (1.5 mg) or placebo and followed for a median duration of 5.4 years. The primary composite endpoint (three-component MACE, as in other CVOTs) occurred in 12.0% of participants receiving dulaglutide and 13.4% placebo subjects, demonstrating statistical superiority for the GLP-1RA (HR 0.88 95% CI 0.79-0.99; p=0.026). An exploratory analysis of REWIND was simultaneously published⁴² to assess the effect of dulaglutide on the renal component of the composite microvascular outcome; this was defined as the first occurrence of new macroalbuminuria (UACR >33.9 mg/mmol [>300 mg/g]), a sustained decline in eGFR of 30% or more from baseline, or chronic renal replacement therapy. At baseline, 791 (7.9%) subjects had macroalbuminuria and mean eGFR was 76.9 mL/min/1.73 m². During follow-up, the renal outcome occurred in 848 (17.1%) participants in the dulaglutide group and in 970 (19.6%) placebo participants (HR 0.85, 95% CI 0.77–0.93; p=0.0004). The major driver was new onset macroalbuminuria (HR 0.77, 95% CI 0.68–0.87; p<0.0001), with HRs of 0.89 (0.78–1.01; p=0.066) for sustained decline in eGFR of 30% or more and 0.75 (0.39–1.44; p=0.39) for chronic renal replacement therapy.

Although the HR for a sustained decline in eGFR of 30% was non-significant, the favourable trend led to the authors performing a series of sensitivity analyses. These showed that dulaglutide was associated with a significantly reduced incidence of a sustained eGFR decline of 40% or more (HR 0.70, 95% CI 0.57–0.85) and 50% or more (HR 0.56, 0.41–0.76). These results are supportive of the findings from the AWARD-7 but, given their post-hoc nature it cannot be concluded that dulaglutide has yet been shown to preserve renal function.

As a result of these data, no dosage adjustment is required in people with mild, moderate or severe renal impairment (eGFR of <90 to ≥15 mL/min/1.73 m²).²⁸⁶ Given that there is very limited experience in people with an eGFR of <15 mL/min/1.73 m² or ESKD, dulaglutide use is not recommended in these individuals.²⁸⁶

Following preliminary results from the AWARD 11 trial, dulaglutide is now licensed in the UK for glucose lowering at doses of 3.0 mg and 4.5 mg once weekly.²⁸⁶ The safety profiles of

these higher doses are consistent with those reported for dulaglutide with no additional renal data reported at the time of this publication. The recommended dose adjustments in renal impairment are identical to the 0.75 mg and 1.5 mg once weekly dosing.

Semaglutide

Semaglutide is a GLP-1RA with an extended half-life of approximately 1 week, permitting once-weekly subcutaneous dosing. The SUSTAIN 6 trial²⁸⁷ was initiated pre-approval and designed to assess non-inferiority of semaglutide compared with a placebo, in terms of cardiovascular safety in people with type 2 diabetes. Overall, 3,297 people 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 participants 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 participants (108 out of 1,648 (6.6%)) compared with the placebo-treated participants (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.

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 people who had a doubling of serum creatinine and/or needed continuous renal replacement therapy was small and similar between groups. A placebo-controlled trial of semaglutide with primary renal endpoints²⁸⁸ is currently ongoing and expected to report in 2024. The primary endpoint for this study is time to first occurrence of a composite of persistent eGFR decline of greater than or equal to 50% from baseline, ESKD (eGFR <15 mL/min/1.73 m², dialysis or transplantation), death from kidney disease or death from cardiovascular disease.

Diabetic retinopathy endpoints were experienced by significantly more people who were treated with semaglutide (50 people (3.0%)) than the placebo (29 people (1.8%)). The reason for this is unknown, but a high baseline prevalence of significant retinopathy, a high baseline HbA1c and a rapid marked decline in blood glucose levels may together have contributed to this outcome.²⁸⁹ A trial specifically designed to investigate the impact of semaglutide on diabetic retinopathy is ongoing,²⁹⁰ recruiting people with type 2 diabetes and Early Treatment Diabetic Retinopathy Study (ETDRS) level of 10–75 (both inclusive) evaluated by fundus photography and confirmed by central reading centre. The primary endpoint of this placebo-controlled trial is the presence of at least three steps ETDRS subject level progression and there are seventeen secondary retinal endpoints. The estimated study completion date is 2025.

According to the summary of product characteristics (SPC),²⁹¹ no dose adjustment of semaglutide is required for people with mild, moderate or severe renal impairment and so it may be used in people with an eGFR of >15 mL/min/1.73 m². Experience with the use of semaglutide in people with severe renal impairment is limited. Semaglutide is not recommended for use in people with ESKD.²⁹¹

An oral form of semaglutide was licensed in the UK in 2020, which is administered once daily. The view of the regulatory bodies appears to be that the safety of the semaglutide

molecule is the same, irrespective of the mode of administration. Hence the renal limitations for oral semaglutide are the same as those for the once weekly injectable formulation.²⁹²

GLP-1RA and insulin co-formulations

Two co-formulations of GLP-1RAs and basal insulin are now available in the UK; Xultophy™ is made up of liraglutide and insulin degludec while Suliqua™ is a combination of lixisenatide and insulin glargine U100. The renal limitations for these fixed ratio formulations are those of their respective GLP-1RAs. There are no current specific trials of these combinations in DKD.

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, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Roche and Sanofi Aventis. He has also received funding for the development of educational programmes from: Elsevier, OmniaMed and Medscape. He is a partner in Glycosmedia, which carries sponsorship declared on its website.
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- Tahseen Chowdhury declares no conflicts of interest.
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- 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.
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List of abbreviations

ACE – angiotensin-converting enzyme
ACR – albumin to creatinine ratio
AKI – acute kidney injury
ARBs – angiotensin-II receptor blockers
ASCVD – atherosclerotic cardiovascular disease
AUC – area under the curve
CAD – coronary artery disease
CBG – capillary blood glucose
CI – confidence interval
CKD – chronic kidney disease
CrCl – creatinine clearance
CSII – continuous subcutaneous insulin infusion
CVD – cardiovascular disease
CVOT – cardiovascular outcome trial
DPP-4 inhibitors – dipeptidyl peptidase-4 inhibitors
DKA – diabetic ketoacidosis
DKD – diabetic kidney disease
eGFR – estimated glomerular filtration rate
ESKD – end-stage kidney disease
GLP-1RAs – glucagon-like peptide-1 receptor agonists
HbA1c – glycated haemoglobin
HDL – high-density lipoprotein
HHF – hospitalisation for heart failure
HR – hazard ratio
MACE – major adverse cardiac event
MALA – metformin-associated lactic acidosis
NPH – neutral protamine Hagedorn
NSAID – non-steroidal anti-inflammatory drug
NYHA – New York Heart Association
OR – odds ratio
SGLT-2 inhibitors – sodium–glucose cotransporter 2
SU – sulfonylurea
TZD – thiazolidinedione
UACR – urine albumin to creatinine ratio

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Appendix A – 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
GLP-1 analogues:	medicine names ending in 'tide' eg exenatide, liraglutide, dulaglutide, lixisenatide and semaglutide
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; GLP-1 = glucagon-like peptide-1 receptor agonists; NSAIDs = non-steroidal anti-inflammatory drugs; SGLT = sodium-glucose cotransporter

Appendix B – Additional user guidance for SGLT-2 inhibitors

SGLT-2 inhibitors, sometimes known as ‘gliflozins’, are blood glucose-lowering drugs that reduce the reabsorption of glucose by the kidneys. They can also help to reduce blood pressure and weight.

These drugs have now also been shown to reduce both kidney and heart failure, independent of the blood glucose-lowering effect.

To avoid low blood glucose (hypoglycaemia), your doses of glucose-lowering medication (such as insulin) and tablets called sulphonylureas (eg gliclazide – Diamicon) may need to be reduced.

If you are taking water tablets (diuretics), and especially if you are at risk of dehydration for any reason, you may need to reduce their dose in discussion with your doctor. Any medication for bladder, prostate or blood pressure control may also need to be reviewed.

Main side effects

Genital fungal (thrush) infections – these are more common in women than men and can usually be treated with over-the-counter medication from a pharmacy.

Slightly greater risk of urinary tract infections – especially if you have a past history of these.

Very uncommon adverse issues

Foot health – if you have been advised you have an ‘at-risk foot’ it is important to clarify with the doctor prescribing your medication if they wish you to start or remain on gliflozins. If you have an active foot problem, such as an infected ulcer or diagnosed active circulatory problem, stop taking gliflozins until you have been advised by your GP or specialist diabetes foot team that it is appropriate to continue.

Diabetic ketoacidosis (DKA) – this is a serious but quite uncommon issue. It may not always be associated with high glucose levels. It can be triggered by an acute illness, infection, starvation, severe carbohydrate restriction, alcohol excess or vomiting. Major dehydration or fasting in preparation for surgery can also be factors, as can missed or excessively reduced insulin dosing (if you are also on insulin therapy). If DKA is suspected, you may be required to have a blood check for ketone levels and kidney function in a healthcare setting. If you have previously experienced an episode of DKA you will usually need to stop taking gliflozins in future.

If you experience any of these uncommon side effects, you should stop taking gliflozins until 1 week after you have fully recovered or as advised by your GP or specialist diabetes team.