

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

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ABSTRACT

A significant percentage of people with diabetes develop chronic kidney disease and diabetes is also a leading cause of end-stage kidney disease (ESKD). The term diabetic kidney disease (DKD) includes both diabetic nephropathy (DN) and diabetes mellitus and chronic kidney disease (DM CKD). DKD is associated with high morbidity and mortality, which are predominantly related to cardiovascular disease.

Hyperglycaemia is a modifiable risk factor for cardiovascular complications and progression of DKD. Recent clinical trials of people with DKD have demonstrated improvement in clinical outcomes with sodium glucose co-transporter-2 (SGLT-2) inhibitors. SGLT-2 inhibitors have significantly reduced progression of DKD and onset of ESKD and these reno-protective effects are independent of glucose lowering. At the time of this update Canagliflozin and Dapagliflozin have been approved for delaying the progression of DKD.

The Association of British Clinical Diabetologists (ABCD) and UK Kidney Association (UKKA) Diabetic Kidney Disease Clinical Speciality Group have undertaken a systematic review and critical appraisal of the available evidence to inform clinical practice guidelines for management of hyperglycaemia in adults with DKD. This 2021 guidance is for the variety of clinicians who treat people with DKD, including GPs and specialists in diabetes, cardiology and nephrology. The full guidelines are endorsed by Diabetes UK and the Royal College of Physicians of London and are available online at <https://abcd.care/position-papers>.

This article is an abridged version of the updated clinical guideline and summarises the key recommendations for practice. For definitions of the evidence grades, see appendix A.

This guideline is based on the opinion of the ABCD and UKKA working group and is an update of previous guidance from 2019; a formal systematic review of the literature was not undertaken. There was no lay input in the development of the guidance, however, the final version was endorsed by Diabetes UK. These recommendations are based on a literature 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 June 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.

Glycaemic targets for the prevention and management of diabetic kidney disease

The management of diabetes is predicated on the basis of reducing hyperglycaemia to improve osmotic 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 optimal benefit remains contentious because, inevitably, the individualised approach to care and the evidence base from different cohorts do not allow clear extrapolation.

People with DKD require multifaceted and comprehensive care and other aspects such as blood pressure and lipid management, are reviewed separately (please see <https://abcd.care/position-papers>)

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 DKD progresses.

Individualised HbA1c targets should be applied in the management of people with DKD, using the levels suggested in **Table 1**. People with DKD are likely to have multiple factors (e.g. anaemia, uraemia, acidosis, reduced circulating albumin levels) which can influence interpretation of HbA1c or alternative glycaemic indices such as fructosamine or glycated albumin. In this setting using capillary glucose measures or continuous blood or flash glucose monitoring may be required. In addition, given the potential for the deterioration of renal function over time, regular monitoring of eGFR is necessary, as this could impact on the type and dosage of diabetes therapies, as well as the appropriate glycaemic target. Furthermore the presence of DKD significantly increases the risk of hypoglycaemia, an effect which is most pronounced as eGFR declines. Consideration of the risks of hypoglycaemia and related patient education on prevention and self-management is required when managing glycaemic control in DKD [1]

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 SGLT-2 inhibitors or GLP-1 receptor agonists where, in addition to glucose lowering, these therapies should be considered in people with DKD where there is an evidence base for cardio-renal protection [1, 2].

Impact of intensification of glycaemic control on DKD in people with 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 42 mmol/mol (6%) (achieved 55 mmol/mol (7.2%)). The study demonstrated reduced incidence of development of microalbuminuria in the intensive control arm [3]. Furthermore, ongoing surveillance for up to 18 years with less intensive glycaemic control (HbA1c subsequently maintained at a mean of 64 mmol/mol (8%)) showed that people in the original intensive group continued to experience lower rates of incident microalbuminuria and macroalbuminuria. They also had less progression to CKD stage 3 (eGFR < 60 mL/min/1.73 m²) and hypertension than the original control group [3]. A country-wide, registry-based observational study from Sweden confirmed increased HbA1c values remain a powerful risk factor for death after adjustment for renal complications, which indicates a residual risk associated with poor glycaemic control [4]. However, all-cause and cardiovascular mortality, 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 [4].

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 [3].

However the burden and risks of hypoglycaemia with tighter glycaemic control has to be considered with this approach and an individualised target should apply.

It may still be reasonable to aim for a HbA1c of 58–62 mmol/mol (7.5–7.8%) in people with type 1 diabetes who have CKD stages 3–4, unless values of 48–58 mmol/mol (6.5–7.5%) are achievable without significant hypoglycaemia risk in those who are younger (below the age of 40 years) (please see levels suggested in **Table 1**). Access to continuous blood or flash glucose monitoring will hopefully enable HbA1c targets to be met while reducing the frequency of hypoglycaemia.

Impact of intensification of glycaemic control on DKD in people with 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.

Two 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 microalbuminuria and macroalbuminuria in people with type 2 diabetes, however there was no significant impact on clinical renal outcomes such as a doubling of serum creatinine, progression to ESKD or death from kidney disease [5, 6]. A more recent meta-analysis implied that intensive glycaemic control had benefits in reducing some renal outcomes but the heterogeneity of glycaemic targets limits the validity of that conclusion [7].

HbA1c targets for people who have type 2 diabetes and DKD.

Individualised HbA1c targets should be applied in the management of people with DKD, using the levels suggested in **Table 1**. These target ranges are based on opinion of the writing committee as there is limited high grade evidence in people with DKD. At present, it would be prudent to consider a HbA1c target of 58 mmol/mol (7.5%) for most people with DKD if their glucose lowering therapies include insulin and a target of up to 68 mmol/mol (8.4%) in older people with more advanced CKD (stage 4 and above). The risks of hypoglycaemia are greater in people with diabetes and CKD especially if people are on insulin treatment or sulphonylurea or glinides. Individualised pragmatic glycaemic goals that balance the benefits and risks of intensive glucose lowering in people with type 2 diabetes DKD and patient education on hypoglycaemia avoidance and self-management are needed.

It remains to be seen whether it is appropriate and safe to have a lower glycaemic HbA1c target of 52 mmol/mol (6.9%) as more GLP-1 and SGLT-2 inhibitor-focused treatments are being used 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.

Renal function measurements in determining medication dosages in diabetes

We 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 [8].

It is important to recognise that eGFR equations have several limitations [9]. There is

also an ongoing important discussion on the continued use of ethnicity in eGFR equations and its potential impact on prescribing practice and clinical care [10].

Glucose-lowering therapies for people who have type 2 diabetes and DKD:

The selection of individual classes of drug, tailored to the additional comorbidities that are frequently seen alongside DKD, will also influence therapy selection (Table 2). In addition, certain combinations of different classes of drugs would need judicious consideration. Although these guidelines focus on individual classes of glucose-lowering drug, combinations of different classes will frequently be prescribed to people with DKD. 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 clinical audit.

Recommendations

- 1 Individualised HbA1c targets should be applied in the management of people with DKD, using the levels suggested in **Table 1**. (Grade 1B).
- 2 Additional comorbidities, that are frequently seen alongside DKD, and risk of hypoglycaemia should also influence therapy selection and HbA1c targets. In people who progress to advanced stages of DKD (eGFR <45 ml/min) or those with fast progression of DKD more frequent monitoring of HbA1c and renal function may be required. (**Table 1 and 2**) (Grade 1B).
- 3 Certain combinations of different classes of drugs need judicious consideration, but appropriate combinations of different classes will frequently be needed to manage DKD (Grade 2D).

Insulin therapy in people with CKD stages 1–3

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

In the early stages of DKD, insulin resistance predominates and may worsen, leading to a greater requirement for insulin. Insulin doses, therefore, are frequently high in early DKD, when albuminuria predominates [11]. As GFR declines, however, insulin requirements diminish, with some studies suggesting a 30% reduction in insulin requirements when the GFR is <60 mL/min/1.73m², compared with when the GFR is >90 mL/min/1.73m² [12].

There are limited data on the use of insulin in mild or moderate DKD with no randomised studies specifically in this population. A meta-analysis of 6-month pooled data from three trials examining the use of insulin glargine U300 in people with CKD (eGFR <60 ml/min) reported 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 in people with DKD [13].

A recent study comparing glargine U300 with insulin degludec U100 in insulin naïve T2DM examined glycaemic effects according to renal status as secondary endpoint. There was a suggestion of greater reduction in HbA1c without an increase in hypoglycaemia in people on glargine U300 in people with eGFR <60 ml/min, but the relatively small number of people with DKD in the study limits any firm conclusions [14].

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

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. In these people, loss of clearance of insulin and reduction in gluconeogenesis in the kidneys leads to a falling insulin requirement and, as a consequence, higher risk of hypoglycaemia. In addition, uraemia-induced anorexia and weight loss may also occur, leading to significant reductions in insulin dosing. Occasionally, insulin requirements may fall low enough to obviate the need for insulin and allow conversion to oral therapy or the cessation of pharmacotherapy altogether. Some guidelines suggest a gradual reduction of the total daily insulin dose to 75% when the GFR is 10–50 mL/min/1.73m², and to 50% for a GFR of <10 mL/min/1.73m² [15].

Insulin therapy in people with ESKD

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 [16].

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 DKD due to increased insulin resistance (Grade 1C).
- 3 As GFR declines, insulin requirements are likely to diminish through reduced renal insulin clearance. Insulin doses should be reduced as GFR falls, 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, reduction of insulin dose should be considered (Grade 1C).

- 4 People who are treated with insulin should undertake regular glucose monitoring (Grade 1C).
- 5 In people who are less 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 experience hypoglycaemia on neutral protamine Hagedorn (NPH) insulin or premixed insulins, conversion to analogue insulins may be of benefit (Grade 1C).

Sulfonylureas

There is very little comparative randomised controlled trial evidence of the use of Sulfonylureas (SUs) in DKD. People with type 2 diabetes and DKD who are on SU treatment are at increased risk of hypoglycaemia. We therefore advise regular capillary blood glucose (CBG) monitoring for people with DKD on SU treatment. All SU should be avoided where possible in advanced renal impairment (e.g. eGFR<30 ml/min/1.73m²). Please see the full guidance document for detailed information on the use of SUs in DKD (<https://abcd.care/position-papers>).

Metformin

Metformin has been used as a first-line oral drug for people with type 2 diabetes for over 60 years. The dose of metformin should be decreased if eGFR is less than 45 mL/minute/1.73m² and omitted if eGFR is less than 30 mL/minute/1.73m². Treatment should be interrupted in people at risk of tissue hypoxia or sudden deterioration in

renal function, for example, dehydration, severe infection, shock, sepsis, acute heart failure, respiratory failure or hepatic impairment, or those who have recently had a myocardial infarction [17].

A recent systematic review suggests that metformin use in moderate DKD (eGFR 30–60 mL/min/1.73m²) confers a mortality benefit of 22% (HR 0.78; 95% CI 0.63–0.96).[18]. Analysis of a community based cohort of 75,413 people showed that metformin was not associated with an increased risk of lactic acidosis in people with eGFR above 30 mL/min/1.73m², but below this level, risk for acidosis was increased by twofold [19]. In contrast another systematic review confirmed the absence of any evidence for an increased risk of lactic acidosis, even in patients with an eGFR <30 mL/min/1.73 m²[20].

We acknowledge lack of high quality evidence for the continued use of metformin in people with eGFR between 25-30 ml/min. Often an individualised and pragmatic approach may be required in people with DKD and eGFR 25-30 ml/min/1.73m² where low dose metformin may be more practical and safer than switching to other glycaemia-lowering drugs such as insulin, which might increase the risk of hypoglycaemia. In this scenario discussion with diabetes and renal specialist teams is required with increased vigilance, education on sick day rules and dose reductions down to 1,000–500 mg/day.

In summary, for most people, the benefits of metformin greatly outweigh the very small lactic acidosis risk: a 30–40% reduction in cardiovascular and diabetes events versus a 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. In recognising that there may be subgroups of people who are at higher risk of lactic acidosis (not just due to

impaired renal function), however, the practical advice for clinicians and people contained in **Table 3** is relevant and in general supports the ongoing use of metformin for people with stable CKD stage 3.

Recommendations

1 Metformin can be used down to an eGFR of 30 mL/min/1.73m² and should be stopped if eGFR is persistently less than 30 mL/minute/1.73m². The dosage should be reduced when the eGFR falls below 45 mL/min/1.73m² (Grade 1B).

2 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 (Grade 1B).

3 Metformin should be withheld prior to and shortly after any procedure that requires the use of radiographic contrast media (Grade 1B).

Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 inhibitors (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 hypoglycaemia and are generally associated with a favourable safety and tolerability profile in people with type 2 diabetes and mild-to-severe renal impairment [21].

Recommendations

1 We recommend that people with DKD of all stages are suitable for treatment with DPP-4 inhibitors (Grade 1B).

- 2 We recommend that doses of DPP-4 inhibitors are appropriately reduced in accordance with the degree of renal impairment (including maintenance haemodialysis) except linagliptin (Grade 1B).
- 3 People with DKD 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 heart failure (Grade 1A).

Pioglitazone

Pioglitazone is one of the few oral glucose-lowering drugs that is licensed for use in people with eGFR of $<30 \text{ mL/min/1.73m}^2$. Pioglitazone should be avoided if there is evidence of heart failure or macular oedema. People should be carefully and regularly monitored for fluid retention. Please see the full guidance for detailed information on the use of pioglitazone in DKD (<https://abcd.care/position-papers>).

Sodium glucose co-transporter-2 inhibitors

Systematic reviews and meta-analyses suggest a clear beneficial class effect of SGLT-2 inhibitors on the risk of cardiovascular disease (CVD) and hospitalisation for heart failure.[22, 23] These benefits are consistently observed in people with DKD even at early stages of disease. In view of high risk of CVD in DKD multifactorial interventions that can reduce the burden of CVD are needed and SGLT-2 inhibitor class offers unique advantages in the context of CVD and renal protection. Recent meta-analyses have demonstrated the beneficial effects of SGLT-2 inhibitors on CVD and renal endpoints (such as dialysis, transplantation and death due to kidney disease) and these effects are seen irrespective of baseline albuminuria, eGFR, HbA1c and are independent of blood glucose-lowering effect or use of renin angiotensin system

(RAS) blockade [22-24] The first evidence that SGLT-2 inhibitors may have renoprotective properties was a secondary analysis of renal endpoints in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG) OUTCOME trial [25]. Subsequent cardiovascular outcome trials (CVOT) with other SGLT-2 inhibitors demonstrated similar renoprotective outcomes which were evaluated as secondary or exploratory outcomes [23]. Within the SGLT-2 inhibitor class, a recent CVOT with Ertugliflozin did not however demonstrate a statistically significant reduction in cardio-renal endpoints [26].

This section focusses in detail on recent outcome trials where renal outcomes were assessed as primary endpoint in DKD and to date only two trials have been published. Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDESCENCE) was the first study of an SGLT-2 inhibitor to have renal outcomes in its primary composite endpoint [27]. 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/1.73m², albuminuria [urine albumin:creatinine ratio (ACR) >33.9–565 mg/mmol (>300 to 5,000 mg/g)] and received RAS blockade. Sixty per cent of recruits had an eGFR of 30–60 mL/min/1.73m². The primary endpoint was a composite of ESKD (dialysis, transplantation, or sustained eGFR of <15 mL/min/1.73m²), 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 ESKD, 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; $p < 0.001$).^[27] Of note, in this high-risk population there was no significant increase in rates of lower limb amputation or fracture, which was only observed with a previous study with canagliflozin but has not reported in CVOTs for dapagliflozin and empagliflozin.

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).^[28] In this study 4,094 participants with an eGFR between 25–75 mL/min/1.73m² and urine ACR 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 RAS blockade although those who were unable to take these medications could be included. The mean baseline eGFR was 41.1 mL/min/1.73m² and the median urine ACR was 107.2 mg/mmol (949 mg/g). The primary outcome was a composite of sustained decline in eGFR of at least 50%, ESKD, or death from renal or cardiovascular causes. The trial was stopped early because of efficacy. 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 eGFR

of at least 50%, ESKD, or death from renal causes was 0.56 (95% CI 0.45 to 0.68; $p < 0.001$). All-cause mortality was 101 in 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 to those without [28].

Practical aspects of using SGLT-2 inhibitors

The observed renal and cardiovascular benefits of SGLT-2 inhibitors are independent of the HbA1c lowering effects of these agents in people with type 2 diabetes and $eGFR > 45 \text{ ml/min/1.73 m}^2$

In people with diabetes and $eGFR < 45 \text{ ml/min/1.73 m}^2$, treatment with SGLT-2 inhibitors do not lower HbA1c significantly. A SGLT-2 inhibitor can be initiated or continued for cardio-renal protection, however, if further glucose lowering is required adding another class of medications to optimise diabetes control is recommended.

If Dapagliflozin or Canagliflozin is started for DKD the medication can be continued until ESKD.

Regardless of urine ACR, we also recommend the initiation of dapagliflozin as licensed for people with diabetes, 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. Please see table 3 and 4 for more detailed information on the use of SGLT-2 inhibitors.

Diabetic ketoacidosis (DKA) secondary to SGLT-2 inhibitor is rare in T2DM with reported incidence between 1 in 1000 to 1 in 10,000 people. In the DAPA-CKD trial no increased risk of DKA was observed with dapagliflozin. However in the CREDENCE trial rates of DKA were higher in the canagliflozin group than in the

placebo group (2.2 vs. 0.2 per 1000 patient-years) [24]. SGLT-2 inhibitor induced DKA can present with normoglycaemia or moderately raised glucose levels. It is important for clinicians to be aware of this so that diagnosis is not missed.

Recommendations

1. We recommend the consideration of SGLT-2 inhibitors in **all** individuals with type 2 diabetes and DKD with an eGFR ≥ 30 mL/min/1.73 m², irrespective of glycaemic control, recognising that this is currently off-licence practice for some drugs in the SGLT-2 inhibitor class. For those with established albuminuria, canagliflozin 100 mg once daily is licenced for renoprotection in DKD and dapagliflozin 10mg can be initiated down to an eGFR of 15 mL/min irrespective of the level of albuminuria (Grade 1A).
2. 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).
3. 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 (expert opinion, no high grade evidence)
4. SGLT-2 inhibitors should be withdrawn in all people who develop DKA. However, if a definitive cause for DKA is identified (e.g. low calorie diet, post-operative catabolic state) reinstatement of SGLT-2 inhibitor may be considered

depending on careful assessment of the individualised risks and benefits by a diabetes specialist. (expert opinion, no high grade evidence)

5. 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 and physiological deterioration and this is not a reason to withdraw the drug. (expert opinion, no high grade evidence). Monitoring of renal function after initiation of agents that are associated with dehydration is an important safety issue and should be performed according to clinical need.

6. We recommend that sick day guidance applies, during which SGLT-2 inhibitors should be temporarily withheld. (expert opinion, no high grade evidence)

Glucagon-like peptide-1 receptor agonists

In 2021, six licensed GLP-1 receptor agonist injectables are available for use in Europe and two involve differing delivery mechanisms for the same molecule (exenatide).

Systematic reviews and meta-analyses suggest a clear beneficial class effect of GLP-1 receptor agonists on the risk of cardiovascular disease (CVD)[22, 29]. CVOT have demonstrated CVD benefits with liraglutide, injectable semaglutide, and dulaglutide. There are currently no primary renal endpoint studies with this class of agent published. However the impact of GLP-1 receptor agonist on renal safety and renal outcomes has been assessed in several studies as secondary or exploratory outcomes. There have been isolated case reports of acute kidney injury (AKI) and interstitial nephritis resulting from exenatide and liraglutide use, and these are referred to in their summary of product characteristics.[30] 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 DKD and acute illness via the temporary cessation of GLP-1RA therapy through general sick day guidance.

The current data on potential reno-protection are based on secondary or exploratory CVOTs. However, a placebo-controlled trial of semaglutide with primary renal endpoints is currently ongoing and expected to report in 2024.

An exploratory analysis of REWIND assessed the effect of dulaglutide on the renal component of the composite microvascular outcome, 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. 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; $p=0.0004$)[31]. 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. Dulaglutide is now licensed in the UK for glucose lowering at doses of 3.0 mg and 4.5 mg once weekly. 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 and the recommended renal threshold is as for the 0.75 mg and 1.5 mg once weekly dosing. No dose adjustment of dulaglutide 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/1.73m². Experience of the use of dulaglutide in people with eGFR <15 is limited and so it is not recommended for use in ESKD.

Secondary analyses of the SUSTAIN 6 trial on renal microvascular outcomes demonstrated a significant reduction of the composite renal endpoint (HR 0.64; CI 0.46–0.88; p=0.005) with semaglutide once weekly.[32] Once again, 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.

According to the summary of product characteristics 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/1.73m². Experience of the use of semaglutide in people with eGFR <15 ml/min is limited and so it is not recommended for use in ESKD. No GLP-1RAs are currently licensed for use in people with CKD stage 5 in the UK, nor for those on renal dialysis.

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.

Recommendations

- 1 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 with GLP-1 RA. There is evidence that treatment with some GLP-1RAs reduce the progression of renal disease in people with type 2 diabetes, but this mainly relates to the new onset of persistent macroalbuminuria (Grade 2B).

- 2 Hence, the main aim of GLP-1 RA therapy in people with DKD should be the improvement of glycaemic control with a low risk of both hypoglycaemia and weight gain (Grade 1A).
- 3 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).
- 4 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).
- 5 People with DKD 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 (sulfonylureas and insulins) (Grade 1A).
- 6 There is no role for the combination of GLP-1 analogues and DPP-4 inhibitors (Grade 1C).

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.

Conclusion

People with DKD have increased risk of morbidity and mortality. Hyperglycaemia is a modifiable risk factor for cardiovascular complications and progression of DKD. Individualised HbA1c targets should be applied in the management of people with DKD, using the levels suggested in this guidance. Delaying ESKD and reducing CVD risk are essential to improve outcomes in this high-risk population. There is now conclusive evidence and consensus that SGLT-2 inhibitors significantly reduce progression of DKD and onset of ESKD in people with Type 2 diabetes and albuminuria. Results of ongoing studies will determine the renal benefits of this class in people with DKD and normo-albuminuria and in people with T1DM.

CONFLICTS OF INTEREST:

- 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.
- Debasish Banerjee was previously funded for research by the British Heart Foundation (BHF). He is funded by ESR AstraZeneca for clinical trials. He has received speaker fees from Vifor Pharma and AstraZeneca
- Tahseen Chowdhury declares no conflicts of interest.
- Dipesh Patel has received honoraria for advisory work and/or lecture fees from AstraZeneca, Boehringer Ingelheim Eli Lilly, MSD and Napp Pharmaceuticals, Novo Nordisk and Sanofi
- Indranil Dasgupta has previously received research grants from Medtronic and Daiichi Sankyo. He has been a member of advisory committees and received

educational grants from AstraZeneca, Amgen, Sanofi, MSD, Pfizer, GSK, Mitsubishi Pharma, Otsuka, Vifor Pharmaceuticals, Fresenius and Roche.

- Parijat De has received honoraria for educational meetings from AstraZeneca, Janssen, Boehringer Ingelheim, Novo, Sanofi, Novartis, Abbott, MSD, Takeda, Roche, Lilly, Ascensia, BD, Internis, GSK, Menarini, Bayer and Besins.
- Patrick Mark has received honoraria from Pfizer, AstraZeneca, Novartis, Bristol Myers Squibb, Napp, Vifor and Pharmacosmos and research support from Boehringer Ingelheim outside this work.
- Damian Fogarty has received honoraria for delivering educational meetings and/or attending advisory boards from AstraZeneca, Sanofi, Vifor Pharmaceuticals and Baxter. He provides consultancy for adjudication of endpoint in RCTs to ACI.
- Andrew Frankel has received research grants, and he prepares educational materials and attends drug advisory boards for: Boehringer Ingelheim/Lilly Alliance, AstraZeneca, Novo Nordisk, Merck and Johnson & Johnson.
- Ana Pokrajac has received honoraria for attending and delivering non-promotional educational meetings and advisory boards from Lilly, NovoNordisk and Boehringer Ingelheim.
- Peter Winocour has received honoraria for delivering educational meetings and/or attending advisory boards for AstraZeneca, Eli Lilly, Novo Nordisk, Sanofi, MSD, Janssen and Vifor Pharmaceuticals.
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- Rosa M Montero no conflicts of interest to declare
- Adnan Sharif has received honoraria for delivering educational meetings and/or attending advisory boards for Boehringer Ingelheim/Lilly Alliance, Napp Pharmaceuticals, Novo Nordisk, Astellas, Sandoz and Atara Biotherapeutics. He currently has grant funding from Chiesi UK.

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Table 1. Proposed Glycaemic targets in people with DKD

Condition	Glycaemic target range	CKD stage and albuminuria	Age
Type 1 diabetes	48–58 mmol/mol (6.5–7.5%)*	CKD stage 2 with variable microalbuminuria	Younger adults (>18) 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 cardio-renal 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

These recommendations are based on opinion of the writing group as there is limited high grade evidence in DKD

Table 2. 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 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

Table 3. Action to be taken for selected medications when treating people with DKD

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.
>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"> Stop Metformin However 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.
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

	<p>combined with diuretics</p> <ul style="list-style-type: none"> those with previous episodes of AKI. <p>*Duration of stopping metformin should be based on the likely period of risk. In general, it should be resumed at a low dose after discharge.</p>
Recovery from AKI	<ul style="list-style-type: none"> Once urine flow has returned to normal and GFR is $>30 \text{ mL/min/1.73 m}^2$, 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 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.
$>60 \text{ mL/min/1.73 m}^2$	<ul style="list-style-type: none"> No renal contraindication to initiation or continuation.
$45\text{--}60 \text{ mL/min/1.73 m}^2$	<ul style="list-style-type: none"> No renal contraindication to initiation or continuation.
$30\text{--}45 \text{ mL/min/1.73 m}^2$	<ul style="list-style-type: none"> Exenatide and lixisenatide to be used ‘with caution’ in people with creatinine clearance 30-50 mL/min, exenatide extended release should be stopped. Liraglutide, dulaglutide and semaglutide have no renal contraindication to initiation or continuation at standard doses.
$<30 \text{ mL/min/1.73 m}^2$	<ul style="list-style-type: none"> Liraglutide, dulaglutide and semaglutide have no renal contraindication to initiation or continuation at standard doses.
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 changes in renal function (a fall in eGFR of $>10 \text{ mL/min/1.73 m}^2$ 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 <ul style="list-style-type: none"> ● have had previous episodes of AKI. <p>*Duration of stopping GLP-1 receptor agonist should be based on the likely period of risk.</p>
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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. ● 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	<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"> ● eGFR < 50 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.
30–45 mL/min/1.73 m²	<ul style="list-style-type: none"> ● 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. • 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 and reno-protection. • Empagliflozin 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 reno-protection and heart failure. • Empagliflozin may be commenced/continued for heart failure • For glucose lowering, current licence recommends against initiation or continuation.
15-30 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. • Empagliflozin may be commenced/continued for heart failure • Dapagliflozin 10mg daily may be commenced/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

	<ul style="list-style-type: none">○ 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>
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		Renal impairment – CKD stage and eGFR (mL/min/1.73 m ²)					
Drug	Class of drug	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			May initiate at 10mg and /or continue for reno-protection and treatment of heart failure	May initiate at 10mg and /or continue for reno-protection and treatment of heart failure	May initiate at 10mg and /or continue for reno-protection and treatment of heart failure Limited experience for treatment of heart failure and reno-protection.	Can be continued at 10mg until renal replacement therapy
Canagliflozin‡	SGLT-2i			May initiate at 100 mg and/or continue for reno-protection	May initiate at 100 mg and/or continue for reno-protection	Continue at 100 mg for reno-protection until renal replacement therapy	
Empagliflozin	SGLT-2i			May initiate at 10mg for treatment of heart failure	May initiate at 10mg for treatment of heart failure	May initiate at 10mg for treatment of heart failure Limited experience for treatment of heart failure	
Ertugliflozin	SGLT-2i			Do not initiate			
Insulin					Dose reduction may be needed	Dose reduction should be needed	Dose reduction should be needed

Table 4: Glucose-lowering therapies – current licensing based on eGFR and cardio-renal protection

CBG = capillary blood glucose. Note that **Sick day guidance** 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. Dapagliflozin** can be initiated for reno-protection down to an eGFR of 15 mL/min/1.73 m² and be continued thereafter until the onset of dialysis or transplantation

Appendix A

Evidence grades for the recommendations

The following evidence grading has been used to determine the strength of the recommendations

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

