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

Summary of recommendations 2018

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Abstract

The ABCD Renal Association guidelines on managing hyperglycaemia in patients with diabetes and kidney disease (DM CKD) are evidence based with recommendations graded accordingly. Audit standards and areas for further research are proposed. Glycaemic targets should vary according to the type of diabetes and the stage of kidney disease. All anti-hyperglycaemic agents can be used in DM CKD but dosage will vary according to the degree of renal disease and certain therapies are currently contraindicated in advanced renal disease. Therefore surveillance for changes in renal function is vital to pre-emptive changes in therapy. Certain combination therapies are either inappropriate of illogical in DM CKD and all with DM CKD should be afforded Sick day Guidance to afford temporary withdrawal of certain therapies. Newer classes of anti-hyperglycaemic agents appear to have renal benefits independent of blood glucose lowering effects but these need clarification from additional studies with hard renal outcomes as primary end points , including evaluation in non–DM CKD.

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Evidence grades for the recommendations

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

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

Search strategy

The recommendations are based on a systematic review of the Cochrane Library, PubMed/MEDLINE, Google Scholar and Embase using the following keywords: type 1 diabetes, insulin, chronic kidney disease, nephropathy, hypoglycaemia, insulin, sulfonylureas, metformin, sodium glucose co-transporter-2 (SGLT-2) inhibitors, pioglitazone, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues and meglitinides.

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Key words: type 1 diabetes, insulin, chronic kidney disease, nephropathy, hypoglycaemia, sulfonylureas, metformin, sodium glucose co-transporter-2 (SGLT-2) inhibitors, pioglitazone, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, meglitinides.

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

The management of diabetes is predicated on the basis of reducing hyperglycaemia to improve hyperglycaemic symptoms, with supportive evidence that this will prevent the onset, and slow down

progression, of renal and vascular complications over time.

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

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

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

By contrast, the more recent European Renal Best Practice guidance in 2015 recognised the lack of prospective randomised trials in CKD stage 3b or worse, and suggested 'vigilant attempts to tighten glycaemic control when [HbA_{1c}] values were >8.5% (69 mmol/mol)' but recommended against tighter glycaemic control, given the hypoglycaemia risk.[4]

A retrospective observational case cohort study found that HbA_{1c} levels of <6.5% (48 mmol/mol) and >8% (63 mmol/mol) were associated with increased mortality in patients with CKD stages 3–4.[5]

The most recent Cochrane Collaborative meta-analysis from 2017 found that there were comparable risks of renal failure, death and major cardiovascular events among patients with stringent glycaemic control (HbA_{1c} <7% (54 mmol/mol)), as opposed to those with less tight control, beyond small clinical benefits on the onset and progression of microalbuminuria.[6]

Type 1 diabetes

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) studied adolescents and adults with type 1 diabetes who were intensively managed for a mean duration of 6.5 years to a target HbA_{1c} of 6% (43 mmol/mol) (achieved 7.2% (55 mmol/mol)). The study clearly demonstrated a reduced incidence for the development and progression of microalbuminuria and macroalbuminuria in the primary and secondary prevention groups.[7] Furthermore, ongoing surveillance for up to 18 years with less intensive glycaemic control (HbA_{1c} subsequently maintained at a mean of 8% (63 mmol/mol)) revealed a legacy effect – that is, the intensive group continued to experience lower rates of incident microalbuminuria and macroalbuminuria but also had less progression to CKD (estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2) and hypertension. At follow-up, however, the intensive group's glycaemic control was indistinguishable from the control group.[8]

At trial entry, none of the subjects in DCCT had CKD (the GFR estimated from creatinine clearance (CrCl) averaged 128 mL/min in both the primary and secondary prevention groups). Urinary albumin excretion was normal in the primary prevention group and was <140 µg/min (mean 14 µg/min) in the secondary prevention group.[7]

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

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

The current UK National Institute for Health and Care Excellence (NICE) guidance to aim for the even tighter target HbA_{1c} of 48 mmol/mol utilises the DCCT target[10] which, although rarely achieved in that study, reduced both the progression of microalbuminuria and normoalbuminuric progression to microalbuminuria. From intervention studies with type 1 diabetes patients who have DN-CKD, there is no current evidence that renal or other outcomes are improved by achieving an HbA_{1c} of 48 mmol/mol.

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

The Joint British Diabetes Societies (JBDS) guidelines for patients with diabetes of any sort who are on haemodialysis recommended HbA_{1c} targets of 58–68 mmol/mol. This was based on U shaped survival curves at values above and below this range and the inherent challenge of assessing glycaemic control in the context of related renal anaemia,[11] which is present in 18–27% of patients with CKD stage 3 and is even more prevalent in those with more advanced CKD.[12,13] The basis for renal anaemia can affect the level of HbA_{1c}, with the normochromic secondary anaemia leading to falsely lower HbA_{1c},[14] while iron deficiency artefactually elevates the HbA_{1c} value.[15]

Type 2 diabetes

With the exception of younger patients who have type 2 diabetes (age <40 years) where the lifetime renal–cardiovascular disease risk

may justify similar glycaemic targets to those for patients with type 1 diabetes, the evidence base for intensive glycaemic control comes from several sources with broadly different trial design and outcomes.

The Steno-2 randomised trial was conducted in 80 patients with microalbuminuria, and reported at intervals over 21 years' follow-up, following a mean of 7.8 years of intensified glycaemic control as part of a package of multiple cardiovascular disease risk factor interventions and lifestyle modification. Although the target HbA_{1c} was set at 48 mmol/mol, the mean HbA_{1c} that was achieved in the study with an insulin-dominant regime was 63 mmol/mol. At various time points there was clear evidence that a reduced number of complications were evolving and developing, including cardiovascular and microvascular (including albuminuric) outcomes.[16,17]

With respect to renal outcomes, in the Steno-2 randomised trial there was a 48% significant risk reduction in the progression to macroalbuminuria through multiple risk factor intervention. Although the sample size was small, there was also a borderline significant reduction in progression to end-stage renal disease (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 HbA_{1c} levels of 58 mmol/l and 59 mmol/l in the intensive and control groups at 21 years' follow-up.[17]

By contrast, the ACCORD study design (with a target HbA_{1c} of 42 mmol/mol and a broadly based intensive insulin regime) found that, at the stage of CKD, intensive glycaemic control led to increased cardiovascular risk and no benefit in terms of the progression of renal disease.[18]

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

The ADVANCE study was a predominantly sulfonylurea-based study and it recorded that intensive glucose control to a target HbA_{1c} of 6.5% (48 mmol/mol) reduced the development and progression of both albuminuric and glomerular filtration outcomes in patients with type 2 diabetes, although the number of events was low.[20] Over 5 years, the numbers needed to treat to prevent one end-stage renal event ranged from 410 participants in the overall study to 41 participants with macroalbuminuria at baseline.[21,22]

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

Two recent meta-analyses demonstrated that, although intensive glucose control (target HbA_{1c} 6.1–7.1% (43–54 mmol/mol)) can lead to a reduced incidence of the surrogate renal measures of microalbuminuria and macroalbuminuria in patients with type 2 diabetes, there was no significant impact on clinical renal outcomes such as a doubling of serum creatinine, progression to end-stage renal disease, death from renal disease or other complications.[23,24] A more recent meta-analysis included data from the Veteran Affairs and UK Prospective Diabetes Study studies to imply that intensive glycaemic control had benefits in reducing these hard renal outcomes, but the heterogeneity of glycaemic targets limits the validity of that conclusion.[25]

Table 1 Glycaemic targets in patients with diabetes and diabetic nephropathy–chronic kidney disease (DN-CKD)

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

GLP-1, glucagon-like peptide-1; SGLT-2, sodium glucose co-transporter-2.

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

The JBDS has already reported and suggested an HbA_{1c} of 58–68 mmol/mol in patients with diabetes who are on haemodialysis, given the hypoglycaemic and cardiovascular safety considerations and the inherent inaccuracy of HbA_{1c}, with falsely lower values in those with anaemia in the context of CKD.[11]

On balance, whereas the lifelong risk that hyperglycaemia will lead to the development and progression of DN-CKD (and other complications) requires a more intensive glycaemic-lowering strategy in those with early onset type 2 diabetes diagnosed before the age of 40, options for intensive glycaemic control after that point with an insulin-intensive regime do not appear to be appropriate with HbA_{1c} levels of <7% (53 mmol/mol).

The recent cardiovascular safety studies with non-insulin-based therapies among cohorts of patients with established cardiovascular disease using empagliflozin and the daily and weekly glucagon-like peptide-1 (GLP-1) analogues included a cohort with established DN-

Table 2 Non-renal and glycaemic contraindications to the selection of blood glucose-lowering therapies in patients with diabetic nephropathy–chronic kidney disease (DN-CKD)

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

GLP-1, glucagon-like peptide-1; SGLT-2, sodium glucose co-transporter-2.

CKD, and found that these patients had less evolution of albuminuria to evident proteinuria with an attained HbA_{1c} of 7.3–7.6% (56–60 mmol/mol).

In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG) study group with the sodium glucose co-transporter-2 (SGLT-2) inhibitor empagliflozin, virtually all had established cardiovascular disease at baseline and all had an eGFR of >30 mL/min/1.73 m^2. CKD stage 3a was present in 17.8% of participants and 7.7% of participants had CKD stage 3b. In addition, 28.7% had microalbuminuria and 11% had macroalbuminuria.[27] The cohort with a reduced eGFR had a baseline HbA_{1c} of 8.1% (65 mmol/mol), which fell to 7.6% (60 mmol/mol) – only 0.3% (3 mmol/mol) lower than the placebo. Thus, despite there being only modest differences in glycaemic control that was not intensified, incident or worsening nephropathy (progression to macroalbuminuria) was reduced by 39%, with a 44% risk reduction in doubling of serum creatinine. Although there were only small numbers, a 55% relative risk reduction in the need for renal replacement therapy was also seen.[27] A more recent evaluation of albuminuria progression confirmed these findings.[28]

In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) study, the majority of participants (72.4%) had cardiovascular disease at entry and 24.7% had CKD. The mean HbA_{1c} of 8.7% (72 mmol/mol) at entry was set against a target HbA_{1c} of 7% (53 mmol/mol), and the achieved HbA_{1c} with liraglutide of 7.6% (60 mmol/mol) was only 0.4% (4 mmol/mol) lower than in the control group. There was a 22% reduction in the incidence of nephropathy, but solely on the basis of proteinuria reduction, with no impact on more advanced renal measures.[29]

In the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN -6) with the weekly GLP-1 analogue semaglutide, the most effective

Table 3 Cautions when using combinations of drug classes to treat diabetes in patients who have chronic kidney disease (CKD)

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

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium glucose co-transporter-2.

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

eGFR level	Medication and action to be taken		
	Pioglitazone	**Metformin**	**Nateglinide and repaglinide**
All patients	• Exclude a past medical history of bladder cancer or uninvestigated haematuria, heart failure or significant fluid retention • Practitioners should weigh up the glycaemic benefit of pioglitazone against the risk of bone fractures • Consider discontinuing pioglitazone in patients who develop osteoporotic fractures	• Practitioners have to weigh up the glycaemic and cardiovascular benefits against the rare risk of associated lactic acidosis • Practitioners should provide all patients with the information leaflet 'Advice for patients taking metformin'	• Practitioners have to weigh up the risk of hypoglycaemia
>60 mL/min/ 1.73 m^2	• No renal contraindication to pioglitazone	• No renal contraindication to metformin • Some of these patients are at increased risk due to other risk factors (see advice for increased vigilance groups in the bottom row of this table)	• Continue or commence nateglinide or repaglinide • Advise patients to monitor their CBG 2 hours after taking the medication and to take precautions when driving
45–60 mL/min/ 1.73 m^2	• Continue use of pioglitazone in patients who are established on the agent but monitor for fluid retention 3–6-monthly thereafter • For new patients who have no major fluid retention, pioglitazone can be started at 15 mg once daily and titrated up, based on the effectiveness and development of fluid retention in 2 weeks	• Continue use in patients who were established on the agent but review the dose in light of glucose control needs • For new patients who have no major active comorbidities, metformin commencement can be considered if age-related life expectancy is normal and vascular/diabetes risks are present • Increase monitoring of renal function (to every 3–6 months).	
30–45 mL/min/ 1.73 m^2	• In patients who are established on pioglitazone, monitor for fluid retention every 3–6-monthly • Patients can be started at 15 mg once daily and titrated up, based on the effectiveness and development of fluid retention in 2 weeks	• Continue or commence metformin with caution and explain the risks and benefits to the patient • Use the lowest dose that achieves glycaemic control (suggest a 50% dose up to 1,000 mg/day) • Closely monitor renal function (every 3 months)	
<30 mL/min/ 1.73 m^2	• In patients who are established on pioglitazone, monitor for fluid retention 3-monthly • Patients can be started at 15 mg once daily and titrated up, based on the effectiveness and development of fluid retention in 2 weeks	• At this level of renal function we cannot give firm recommendations about the ongoing use of metformin • Some specialists may choose to use the agent in selected patients where they see that the benefits outweigh the risks • Pharmacokinetic work would suggest that, if metformin is used, a dose of 500–1,000 mg/day would result in 95% of people having peak metformin concentrations of <5 mg/L • Consider measuring the true GFR directly, especially in patients who are obese. The Cockcroft–Gault formula may give a better reflection of eGFR in obese patients and may allow the safe use of metformin in patients who have a low GFR	• Review the dose of nateglinide or repaglinide if the patient is already taking it, and consider a reduction based on their CBG • Advise patients to monitor their CBG 2 hours after taking medication and to take precautions when driving • Commence nateglinide or repaglinide at half the regular dose
Dialysis	• Patients 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 patients who are established on pioglitazone, monitor for fluid retention 3-monthly		• Not licensed but not contraindicated, so it can be considered • Continue or commence repaglinide at half the regular dose • Advise patients to take precautions when driving • Increased monitoring is required while a patient is on these agents

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

eGFR level	Medication and action to be taken
	Metformin
AKI (or at risk of AKI)	Review and consider (temporarily) stopping* metformin in patients who: • have acute changes in renal function (a fall in eGFR of 10 mL/min/1.73 m^2 over a period of days or weeks) • are at risk of AKI such as: o acute volume depletion and dehydration (eg, gastrointestinal upset, stomas, change in diuretic dose) o during operative procedures with a high risk of hypotension or volume depletion o in the presence of hypotension or shock (eg, severe infection) o intravascular administration of iodinated contrast agents (stop metformin on the day of and 2 days after X-ray-related intravenous contrast use) o co-administration with nephrotoxic drugs (eg, NSAIDs) o patients with acute illness who are also on drugs that are known precipitants of AKI in association with any angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (such as NSAIDs), especially combined with diuretics • those with previous episodes of AKI.
Recovery from AKI	• Once urine flow has returned to normal and GFR is >30 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	Increased vigilance is needed for the following groups of patients who are likely to be at a higher risk of lactic acidosis even with normal renal function: • those with decompensated cardiac or respiratory failure • those with acute conditions that may cause tissue hypoxia (eg, recent myocardial infarction or shock) • those with hepatic insufficiency, acute alcohol intoxication or alcoholism

*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.
AKI, acute kidney disease; CBG, capillary blood glucose; eGFR, estimated glomerular filtration rate; NSAID, non-steroidal anti-inflammatory drug.

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 HbA_{1c} at baseline of 8.7% (72 mmol/mol), the active treatment led to a reduction in HbA_{1c} to 7.3–7.6% (56–60 mmol/mol) depending on the dosage, which was 0.7–1% (7–10 mmol/mol) lower than the control group. New or worsening nephropathy was reduced by 36% with active treatment, essentially through a reduction in progression to macroalbuminuria.[30]

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

The following sections focus in more detail on the available glucose-lowering therapies for patients who have diabetes and DN-CKD.

At present, it would be prudent to consider an HbA_{1c} target of 58 mmol/mol for most patients with type 2 diabetes and DN-CKD if they are on an insulin-dominant regime, and a target of up to 68 mmol/mol in older patients with more advanced CKD, especially where they have renal anaemia.

It remains to be seen whether it is appropriate and safe to have a lower glycaemic HbA_{1c} target of 52 mmol/mol in patients who are treated with less insulin and more GLP-1- and SGLT-2 inhibitor-focused treatments when the eGFR is >30 mL/min/1.73 m^2, both when a patient does and does not have cardiovascular disease.

From the current evidence, there is no basis to seek HbA_{1c} values of lower than 52 mmol/mol in older patients with type 2 diabetes and DN-CKD.

Conclusions

Individualised HbA_{1c} targets should be applied in the management of patients with diabetes and DN-CKD using the levels suggested in Table 1. It is, however, important to ensure that anaemia has been excluded or considered when using HbA_{1c} to assess glycaemia. In addition, given the potential for the deterioration of renal function over time, at least annual monitoring of GFR is necessary, as this could impact on the type and dosage of diabetes therapies, as well as the appropriate glycaemic target. The selection of individual classes of agent, tailored to the additional comorbidities that are frequently seen alongside DN-CKD, will also influence therapy

selection (Table 2). In addition, certain combinations of different classes of agents would need judicious consideration (Table 3). Although these current guidelines focus on the individual classes of glucose-lowering agent, combinations of different classes will frequently be used to manage diabetes in patients with CKD. There is a relative dearth of studies that specifically evaluate different drug combinations in patients with kidney disease, and this is clearly an area for both further research and current clinical audit (Table 4).

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

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

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

Areas that require further research

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

Audit standards

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

3. Sulfonylureas

Recommendations

1. Patients with type 2 diabetes and CKD who are on sulfonylurea treatment are at increased risk of hypoglycaemia. We therefore advise regular capillary blood glucose (CBG) monitoring in this patient group. For patients who have an eGFR of <45 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 sulfonylureas for patients with type 2 diabetes and CKD. Given the absence of excess cardiovascular events in a randomised trial, gliclazide should be the preferred choice of drug (Grade 1B).
3. We suggest that a sub-maximal dosage of gliclazide and glipizide is used in patients with an eGFR of <45 mL/min/1.73 m^2 (Grade 2B).
4. We suggest that sulfonylureas should be avoided alongside insulin in patients with an eGFR of <45 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 patient's eGFR is <30 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 patients with CKD, and we suggest that they should be avoided in such patients (Grade 2B).

Areas that require further research

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

Audit standards

1. The proportion of patients with CKD who are on sulfonylureas and who regularly monitor their CBG.
2. The proportion of patients with an eGFR of <30 mL/min/1.73 m^2 who are on sulfonylureas and who regularly monitor their CBG.
3. The proportion of patients who are on individual sulfonylureas according to CKD stage and frequency of severe acute hypoglycaemic episodes (SAHE) who have recorded ambulance call outs and hospital admissions.
4. The proportion of patients with an eGFR of <60 (and <45) mL/min/1.73 m^2 who are on sulfonylureas, and the dosage used.
5. The proportion of patients with an eGFR of <60 (and <45) mL/min/1.73 m^2 who are on sulfonylureas in combination with insulin therapy who have an HbA_{1c} of 53 mmol/mol (<6.5%).
6. The documented sick day guidance that is provided to patients with CKD who are on sulfonylureas and other agents.

4. Meglitinides

Recommendations

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

Areas that require further research

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

Audit standards

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

5. Metformin

Recommendations

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

Areas that require further research

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

Audit standards

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

6. Pioglitazone

Recommendations

1. We recommend that patients with type 2 diabetes and CKD of all stages can be considered for treatment with pioglitazone (Grade 1B).
2. Pioglitazone should be avoided if there is evidence that a patient has heart failure or macular oedema (Grade 1B).
3. Caution is required when commencing treatment in patients who have evidence of fluid overload. These patients should be

monitored for fluid retention initially after 2 weeks, and 3–6-monthly thereafter (Grade 1C).
4. We advise that patients with CKD who gain more than 20% of their body weight within the first 2 weeks should discontinue pioglitazone (Grade 2C).
5. Caution is recommended when introducing pioglitazone in patients who have an increased risk of hip fractures (Grade 1C).
6. Consider discontinuing pioglitazone in patients who develop hip fractures while they are on pioglitazone (Grade 1D).
7. Do not start pioglitazone in patients who have known bladder cancer (Grade 1B).
8. We suggest the discontinuation of pioglitazone in patients who have painless haematuria until bladder cancer is excluded. This reflects the current 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 further research

1. The head-to-head comparison of pioglitazone with other oral hypoglycaemic agents, in terms of safety and efficiency, across the range of eGFRs.
2. The safety and efficiency of pioglitazone in combination with sodium glucose co-transporter-2 (SGLT-2) receptor blockers. For example, the benefits of the volume-reducing effect of SGLT-2 for pioglitazone-induced fluid retention; cardiovascular risk reduction; the effect on bone fractures; and the risks of urinary tract cancers with increased exposure to high glucose concentrations.
3. The risk of bone fractures in patients who are on pioglitazone in comparison with other therapies in patients who have type 2 diabetes and CKD.
4. The efficacy and safety of pioglitazone as a third-line oral therapy in patients with type 2 diabetes and CKD.
5. The efficacy and safety of pioglitazone use with background insulin in patients with type 2 diabetes.
6. The potential cardiovascular benefit of pioglitazone treatment in patients with type 2 diabetes and chronic heart failure, where fluid retention is controlled by diuretics.
7. The rate of renal function decline in patients with type 2 diabetes who are taking pioglitazone.

Audit standards

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

7. Dipeptidyl peptidase-4 (DPP-4) inhibitors

Recommendations

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

Areas that require further research

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

Audit standards

1. The proportion of patients with type 2 diabetes and CKD who are taking DPP-4 inhibitors, according to the degree of renal impairment and across the ranges of eGFR, including those who are on maintenance haemodialysis.
2. The proportion of patients with type 2 diabetes and CKD who are taking appropriate doses of DPP-4 inhibitors, according to their degree of renal impairment.
3. The proportion of patients with type 2 diabetes and CKD who are attaining the recommended target HbA_{1c} with DPP-4 inhibitors as mono, dual and triple therapy, including insulin, according to their stage of CKD.
4. The proportion of patients with type 2 diabetes and CKD who are sustaining the recommended target HbA_{1c} with DPP-4

inhibitors as mono, dual and triple therapy, including insulin, according to their stage of CKD.
5. The proportion of patients with type 2 diabetes and CKD who are taking DPP-4 inhibitors who show a percentage reduction in albuminuria.
6. The comparative efficacy of DPP-4 inhibitors in patients with type 2 diabetes and CKD across the range of eGFRs.
7. The incidence of hospitalisation of patients with heart failure who have type 2 diabetes and CKD and are being treated with DPP-4 inhibitors.
8. The efficacy of glycaemic control (HbA_{1c} reduction) with reduced doses of DPP-4 inhibitors in patients with progressive renal impairment.

Areas of concern

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

8. Sodium glucose co-transporter-2 (SGLT-2) inhibitors

Recommendations

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

Areas that require further research

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

9. Glucagon-like peptide-1 receptor agonists (GLP-1RAs)

Recommendations

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

Areas that require further research

1. There is a need for studies on GLP-1RAs that have hard renal endpoints as their primary outcome (current studies have a pri-

Key messages

- Tailor management of hyperglycaemia according to type of diabetes and severity of renal disease
- Consider non-glycaemic benefits and adverse effects in selection of different classes of anti-hyperglycaemic agents
- Ensure combination therapy is appropriate for those with renal disease and re-evaluate dosage if renal function deteriorates
- Ensure Sick Day Guidance is provided to all with diabetes and renal disease

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

Audit standards

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

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References

1. National Institute for Health and Care Excellence (NICE). Type 2 diabetes in adults: management. [NG28]. London: NICE, 2015. www.nice.org.uk/guidance/ng28 (accessed Feb 2018).
2. Herman WH, Kalyani RR, Wexler DJ, Matthews DR, Inzucchi S. Approaches to glycaemic treatment. Standards of medical care in diabetes – 2016. *Diabetes Care* 2016;**39**(Suppl 1):S52–9. https://doi.org/10.2337/dc16-S010
3. National Kidney Foundation. KDOQI (Kidney Disease Outcomes Quality Initiative) clinical practice guideline for diabetes and CKD: 2012 update. *Am J Kidney Dis* 2012;**60**:850–86. https://doi.org/10.1053/j.ajkd.2012.07.005
4. Bilo H, Coentrao L, Couchard C, *et al*. Clinical practice guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min). *Nephrol Dial Transplant* 2015;**30**(Suppl 2):1–142. https://doi.org/10.1093/ndt/gfv100
5. Shurraw S, Hemmelgam B, Lin M, *et al*. Association between glycemic control and adverse outcomes in people with diabetes mellitus and chronic kidney disease: a population based cohort study. *Arch Intern Med* 2011;**171**:1920–7. https://doi.org/10.1001/archinternmed.2011.537
6. Ruospo M, Saglimbene VM, Palmer SC, *et al*. Glucose targets for preventing diabetic kidney disease and its progression. *Cochrane Database Syst Rev* 2017;**6**:CD010137. https://doi.org/10.1002/14651858.
7. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;**329**:977–86.
8. De Boer IH, for the DCCT /EDIC Research Group. Kidney disease and related findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications. *Diabetes Care* 2014;**37**:24–30. https://doi.org/10.2337/dc13-2113
9. Lind M, Svensson AM, Kosiborod M, *et al*. Glycemic control and excess mortality in type 1 diabetes. *N Engl J Med* 2014;**371**:1972–82. https://doi.org/10.1056/NEJMoa1408214
10. National Institute for Health and Care Excellence (NICE). Type 1 diabetes in adults: diagnosis and management. [NG17]. London: NICE, 2015. www.nice.org.uk/guidance/ng17 (accessed Feb 2018).
11. Frankel A, Kazempour-Ardebili S, Bedi R, *et al*. Management of adults with diabetes on the haemodialysis unit: summary of new guidance from the Joint British Diabetes Societies (JBDS) and the Renal Association. *Br J Diabetes* 2016;**16**:69–77. https://doi.org/10.15277/bjd.2016.073
12. Raja UY, Chan J, Radford E, *et al*. The prevalence of anaemia in diabetes with stage 3 chronic kidney disease: a retrospective analysis. *Br J Diabetes Vasc Dis* 2011;**11**:259–61.
13. New JP, Aung T, Baker PG, *et al*. The high prevalence of unrecognized anaemia in patients with diabetes and chronic kidney disease: a population-based study. *Diabet Med* 2008;**25**:564–9. https://doi.org/10.1111/j.1464-5491.2008.02424.x
14. Agarwal R, Light RP. Relationship between glycosylated haemoglobin and blood glucose during progression of chronic disease. *Am J Nephrol* 2011;**34**:32–41. https://doi.org/10.1159/000328737
15. Ng JM, Cooke M, Bhandari S, Atkin SL, Kilpatrick ES. The effect of iron and erythropoietin treatment on the A1C of patients with diabetes and chronic kidney disease. *Diabetes Care* 2010;**33**:2310–3. https://doi.org/10.2337/dc10-0917
16. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifac-

torial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003;**348**:383–93.
17. Gaede P, Oellgaard J, Carstensen B, *et al*. Years of life gained by multifactorial intervention in patients with type 2 diabetes and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial. *Diabetologia* 2016;**59**:2298–307. https://doi.org/10.1007/s00125-016-4065-6
18. Papademetriou V, Lovato L, Doumas M, *et al*, for the ACCORD Study Group. Chronic kidney disease and intensive glycaemic control increase cardiovascular risk in patients with type 2 diabetes. *Kidney Int* 2015;**87**:649–59. https://doi.org/10.1038/ki.2014.296
19. Ismail-Beigl F, Craven T, Banerji MA, *et al*, for the ACCORD Trial Group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet* 2010;**376**:419–30. https://doi.org/10.1016/S0140-6736(10)60576-4
20. Perkovic V, Heerspink HL, Chalmers J, *et al*, for the ADVANCE Collaborative Group. Intensive glucose control improves kidney outcomes in patients with type 2 diabetes. *Kidney Int* 2013;**83**:517–23. https://doi.org/10.1038/ki.2012.401
21. Zoungas S, Chalmers J, Neal B *et al*, for the ADVANCE Collaborative Group. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med* 2014;**371**:1392–406. https://doi.org/10.1056/NEJMoa1407963
22. Wong MG, Perkovic V, Chalmers J, *et al*, for the ADVANCE-ON Collaborative Group. Long-term benefits of intensive glucose control for preventing end-stage kidney disease: ADVANCE-ON. *Diabetes Care* 2016;**39**:694–700. https://doi.org/10.2337/dc15-2322
23. Coca SG, Ismail-Beigi F, Haq N, Krumholz HM, Parikh CR. Role of intensive glucose control in development of renal end points in type 2 diabetes: systematic review and meta-analysis intensive glucose control in type 2 diabetes. *Arch Intern Med* 2012;**172**:761–9. https://doi.org/10.1001/archinternmed.2011.2230
24. Rodriguez-Gutiérrez R, Montori VM. Glycaemic control for patients with type 2 diabetes mellitus: our evolving faith in the face of evidence. *Circ Cardiovasc Qual Outcomes* 2016;**9**:504–12. https://doi.org/10.1161/CIRCOUTCOMES.116.002901
25. Zoungas S, Arima H, Gerstein HC, *et al*, Collaborators on Trials of Lowering Glucose (CONTROL) Group. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. *Lancet Diabetes Endocrinol* 2017;**5**:431–7. https://doi.org/10.1016/S2213-8587(17)30104-3
26. Lo C, Toyama T, Hirakawa Y, *et al*. Insulin and glucose-lowering agents for treating people with diabetes and chronic kidney disease (Protocol). *Cochrane Database of Systematic Reviews* 2015(8). https://doi.org/10.1002/14651858
27. Wanner C, Inzucchi SE, Lachin JM, *et al*, for the EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016;**375**:323–34. https://doi.org/10.1056/NEJMoa1515920
28. Cherney DZI, Zinman B, Inzucchi SE, *et al*. Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2017;**5**:610–21. https://doi.org/10.1016/S2213-8587(17)30182-1
29. Marso SP, Daniels GH, Brown-Frandsen K, *et al*, on behalf of the LEADER trial investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;**375**:311–22. https://doi.org/10.1056/NEJMoa1603827
30. Marso SP, Bain SC, Consoli A, *et al*, for the SUSTAIN Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;**375**:1834–44. https://doi.org/10.1056/NEJMoa1607141
31. Wang Y, Katzmarzyk PT, Horswell R, Zhao W, Johnson J, Hu G. Comparison of the heart failure risk stratification performance of the CKD-EPI equation and the MDRD equation for estimated glomerular filtration rate in patients with type 2 diabetes. *Diabet Med* 2016;**33**:609–20. https://doi.org/10.1111/dme.12859
32. Nair S, Mishra V, Hayden K, *et al*. The four-variable modification of diet in renal disease formula underestimates glomerular filtration rate in obese type 2 diabetic individuals with chronic kidney disease. *Diabetologia* 2011;**54**:1304–7. https://doi.org/10.1007/s00125-011-2085-9

Appendix A: Antihyperglycaemics in chronic kidney disease (CKD)

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

* Sick day guidance

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

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

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

Appendix B: Medicines sick day guidance

Medicines sick day guidance

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

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

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

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

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

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

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

Medications to omit temporarily

Metformin

SGLT-2 inhibitors:	medicine names ending in 'flozin' eg canagliflozin, dapagliflozin and empagliflozin
GLP-1 analogues:	medicine names ending in 'tide' eg exenatide, liraglutide, dulaglutide and lixisenatide
ACE inhibitors:	medicine names ending in 'pril' eg lisinopril, perindopril and ramipril
ARBs:	medicine names ending in 'artan' eg losartan, candesartan and valsartan
NSAIDs:	anti-inflammatory painkillers eg ibuprofen, diclofenac and naproxen
Diuretics:	sometimes called 'water pills' eg furosemide, indapamide, bendroflumethiazide, bumetanide and spironolactone

ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; GLP-1 = glucagon-like peptide-1; NSAIDs = nc steroidal anti-inflammatory drugs; SGLT = sodium-glucose cotransporter.