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For Healthcare professionals:

TYPE 2 DIABETES AND CHRONIC KIDNEY DISEASE

Endorsed by:



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FOREWORD

The combination of diabetes and chronic kidney disease often has a devastating impact on the individual affected. Improving the accuracy of clinical care for patients with diabetes and CKD is a major opportunity to help those affected, as there are strong signals that we could be much better at monitoring albuminuria and eGFR and using established and new treatments consistent with the evidence for their effectiveness. This guidance, written by June James, James Burton, Debbie Hicks, and Jill Hill for TREND-UK provides a succinct and expert summary that will help address these shortfalls through assisting you in your understanding of the area including the evidence for the management of patients with diabetes and CKD. I commend it to you.

Professor Paul Cockwell

Clinical Vice President, UK Renal Association
Medical co-chair, Kidney Quality Improvement Partnership (KQuIP)

Almost one in five people living with diabetes will need treatment for kidney disease in their lifetime, and in the UK today more than ten thousand people with diabetes have end stage kidney failure today. That's why it's absolutely vital that frontline healthcare professionals have the skills, tools and information they need to support their patients in this critical area of diabetes care.

This fantastic new guidance from TREND-UK gives healthcare professionals the essential, up-to-date information they need to support the kidney health of patients living with diabetes. Helping healthcare professionals to be kidney-aware, has the potential to prevent many thousands of people with diabetes from developing serious complications with their kidneys, and will ensure those who experience nephropathy get the best support possible to manage it.

Diabetes UK warmly welcomes this guidance, we hope that healthcare professionals use this resource to enhance the diabetes care they give to their patients.

Chris Askew

Chris Askew, CEO Diabetes UK.

Acknowledgments:

Dr Rob Gregory and Helen Sharp



ABOUT THIS GUIDANCE

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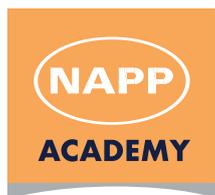
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About TREND-UK

TREND-UK is a working group of diabetes nurses with different skills and backgrounds, set up in 2009 in response to a request by the diabetes tsar at that time for a collective voice that represented all diabetes nursing groups. The original founding co-chairs of TREND-UK were experienced nurse consultants, working in a variety of settings and closely involved with most of the organisations representing nurses working with people with diabetes. TREND-UK has produced a number of resources for nurses and people with diabetes, available on www.trend-uk.org. Registration to access these is free of charge and available to anyone interested in caring for people with diabetes as well as those with the condition.

The creation of this guidance was supported by:



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RATIONALE AND REMIT

Diabetes and chronic kidney disease are both common long-term conditions. Each has an adverse impact for people living with either condition. When combined, the impact on the individual and their families can lead to significant social and financial hardship as well as increasingly poor health and early death in the person affected. Diabetes and chronic kidney disease are associated with cardiovascular disease, neuropathy and retinopathy. Diabetes is the commonest cause of end stage renal disease and accounts for 28.6% of people receiving renal replacement therapy (Hole et al 2018). Effective management of glycaemia, blood pressure and lipids can delay the progression of long-term complications such as nephropathy (Holman et al 2008).

If health care professionals are to make a difference in delaying progression of CKD in people with diabetes, they need to understand more about the condition and how chronic kidney disease impacts on both lifestyle and use of commonly used antihyperglycaemic agents.

When implementing this guidance, full account should be taken of the local context and any action taken should be in line with statutory obligations required of the organisation and individual. No part of this guidance should be interpreted in a way that would knowingly put any person at risk.



INTRODUCTION TO CHRONIC KIDNEY DISEASE (CKD) IN TYPE 2 DIABETES

More than 3.8 million people in the UK have diabetes and 1.1 million do not know they have it. By 2025 it is predicted that over 5 million people in the UK will have diabetes (Diabetes UK, 2017). Diabetes costs the National Health Service (NHS) £10 billion per year and 80% of this is spent on complications such as nephropathy, retinopathy, cardiovascular disease and diabetic foot disease (NHS England, 2012).

Three million people in the UK are estimated to have CKD. 64,887 adult patients were receiving renal replacement therapy (RRT) for end stage kidney disease (ESKD) in the UK on 31/12/2017, an increase of 3.0% from 2016. 8001 patients started RRT in 2017, a 2.6% increase from 2016. (Hole et al 2018). The cost to the NHS of CKD in 2009-2010 was £1.45 billion in the UK and 50% of this was spent on renal replacement therapy (Kerr 2012).

Around 40% of people with diabetes (both type 1 and type 2) will develop microalbuminuria during their lifetime, an early indicator of damage to the kidneys. Of those, 18-30% will go on to develop more significant CKD classified as between stages 3-5. Unchecked, this can progress and in the UK 29% of people starting renal replacement therapy have diabetes as the primary cause of their kidney failure (Hole et al 2018).

What is CKD?

CKD is defined as abnormalities of the kidney structure or function that are present for >3 months, with implications for health (KDIGO 2012).

Diabetic nephropathy (diabetic kidney disease: DKD) is a sub-type of CKD seen in people with diabetes; this is defined as deterioration of the functioning of the kidneys from long-standing diabetes, usually in the presence of albuminuria (medicinenet.com, accessed 2018).

Diagnosis

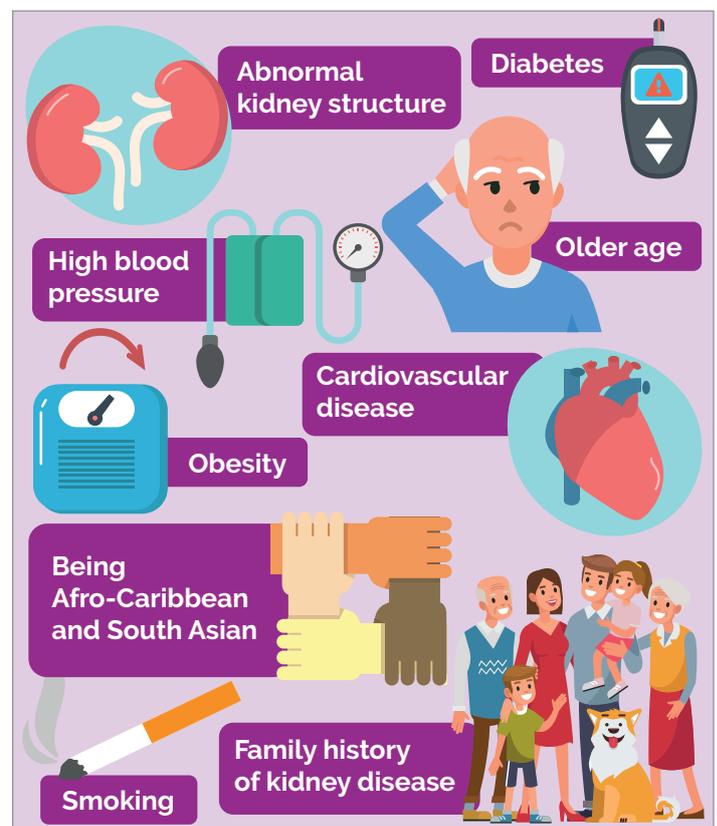
The diagnosis of CKD can be made in two ways; using the creatinine estimated glomerular filtration rate (eGFR) or urine albumin to creatinine ratio (ACR). The ACR can indicate CKD before a falling eGFR is seen. An early morning sample of urine is recommended for the assessment of the ACR. If this is not available a sample obtained later in the day can still be used.

Two eGFR estimations
<math><60\text{ml}/\text{min}/1.73\text{m}^2</math>
over a period of at least
90 days (with or without
markers of kidney
damage)¹

Normal eGFR with urine
albumin to creatinine
ratio (ACR)
>3 mg/mmol¹

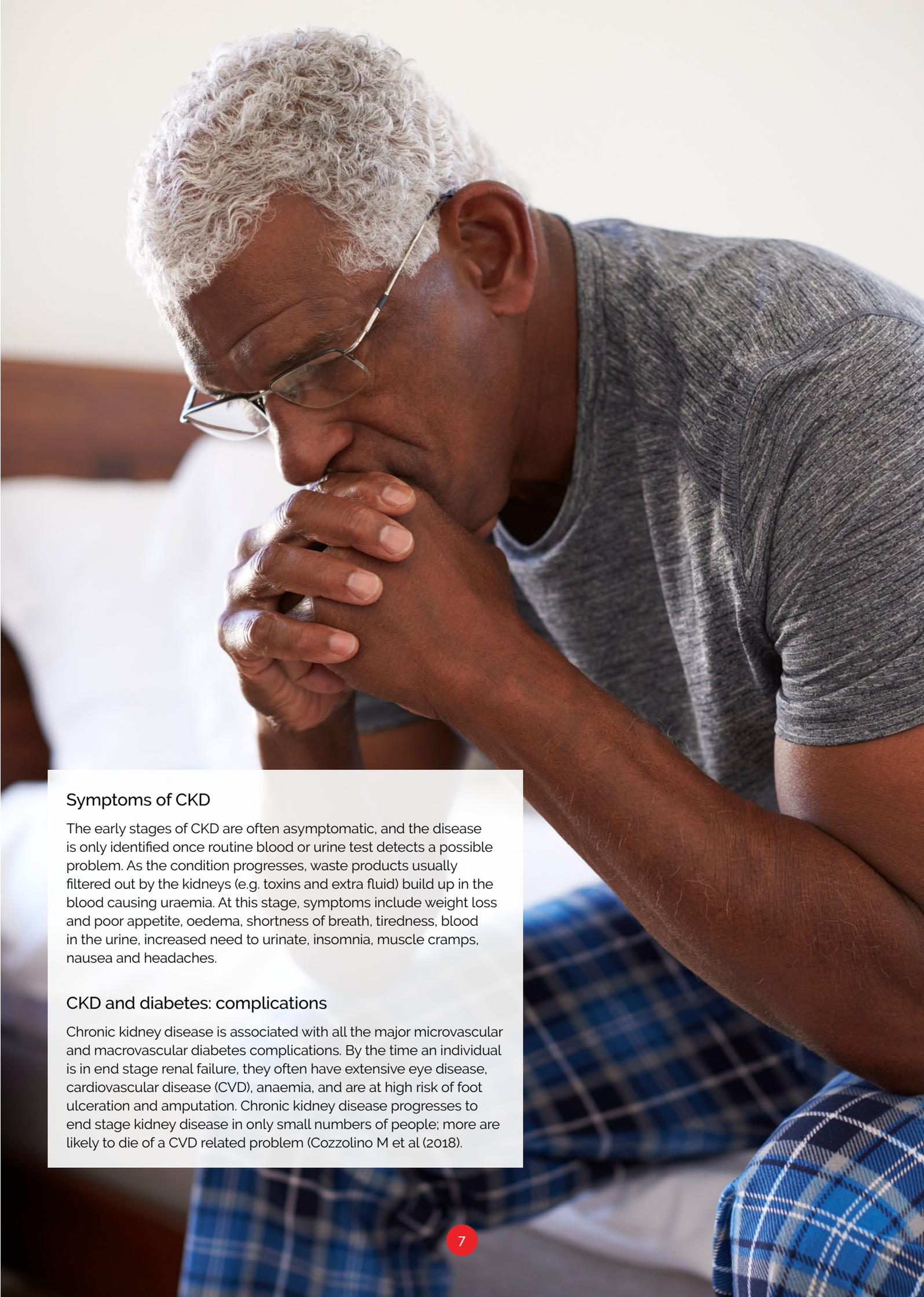
Table 1: Causes of chronic kidney disease (Mayoclinic.org 2019)

>	Type 1 or type 2 diabetes
>	Recurrent urine infection
>	Hypertension
>	Interstitial nephritis
>	Glomerulonephritis
>	Autosomal dominant polycystic kidney disease (ADPKD)
>	Prolonged obstruction of the urinary tract, from conditions such as enlarged prostate, kidney stones and some cancers
>	Vesicoureteral reflux, where urine is forced backed into the kidneys when the bladder contracts
>	Prolonged use of specific medications including non steroidal anti-inflammatory agents (NSAIDs) calcineurin inhibitors, lithium and, NSAIDs



The causes of chronic kidney disease are shown in Table 1

Figure 1 ;The risk factors for CKD (Mayoclinic.org 2019)



Symptoms of CKD

The early stages of CKD are often asymptomatic, and the disease is only identified once routine blood or urine test detects a possible problem. As the condition progresses, waste products usually filtered out by the kidneys (e.g. toxins and extra fluid) build up in the blood causing uraemia. At this stage, symptoms include weight loss and poor appetite, oedema, shortness of breath, tiredness, blood in the urine, increased need to urinate, insomnia, muscle cramps, nausea and headaches.

CKD and diabetes: complications

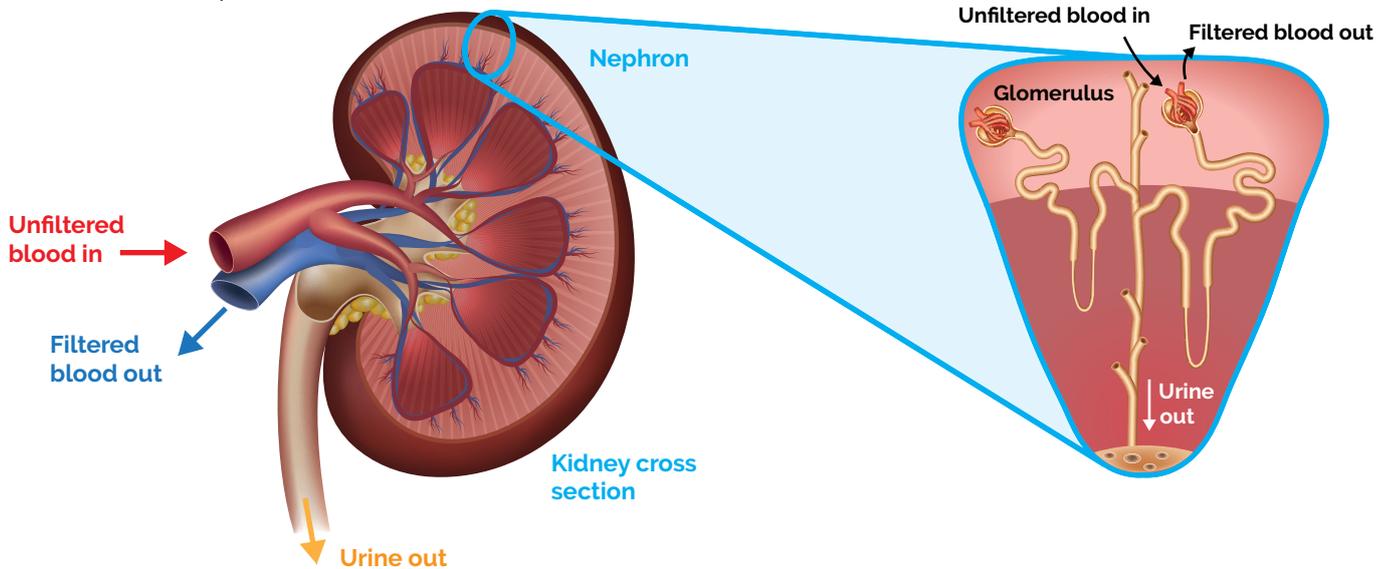
Chronic kidney disease is associated with all the major microvascular and macrovascular diabetes complications. By the time an individual is in end stage renal failure, they often have extensive eye disease, cardiovascular disease (CVD), anaemia, and are at high risk of foot ulceration and amputation. Chronic kidney disease progresses to end stage kidney disease in only small numbers of people; more are likely to die of a CVD related problem (Cozzolino M et al (2018)).

How do the kidneys work?

The kidneys filter waste and excess fluids from the blood, which are then excreted in urine. When chronic kidney disease reaches an advanced stage, dangerous levels of fluid, electrolytes and waste can build up in the body (mayoclinic.org). The kidneys:

- Filter 240-300 pints of blood a day to produce 2-4 pints of urine
- Make the hormone Erythropoietin which stimulates the bone marrow to produce red blood cells
- Make an active form of Vitamin D to make healthy bones
- Maintain the acid-base balance of the body

Figure 2: Parts of the nephron



The stages of chronic kidney disease

The CKD stages are aligned to the individuals' eGFR and albumin: creatinine ratio (ACR). Table 3 shows the different stages

Table 2: Kidney Disease: Improving Global Outcomes (KDIGO) CKD work group 2013)

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased <30 mg/g <3 mg/mmol	Moderately increased 30-300 mg/g 3-30 mg/mmol	Severely increased >300 mg/g >30 mg/mmol
GFR categories (mL/min/1.72 m ²) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45- 59			
	G3b	Moderately to severely decreased	30- 44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

- ⚠ Most individuals are not characterised as having CKD unless the eGFR is less than 60 mL/min/1.73²
- ⚠ Be aware that some laboratories are only reporting the actual eGFR reading in people unless their eGFR is below 60 mL/min/1.73². Reporting in this way means any change in trend cannot be identified
- ⚠ Once the eGFR is below 60 mL/min/1.73² 40% of kidney function has already been lost so always request the full result

SCREENING AND MONITORING FOR CKD

People with diabetes should have their eGFR and ACR measured at least annually. However, there are different determinants that need to be considered when assessing for CKD. These include:

- The underlying cause of CKD
- Past trends in creatinine based eGFR and ACR (but be aware that CKD progression is often non-linear)
- Comorbidities, especially heart failure
- Changes to their treatment (such as renin-angiotensin-aldosterone system [RAAS] antagonists, NSAIDs and diuretics)
- Nutritional advice related to diabetes and CKD
- Intercurrent illness
- Whether they have chosen conservative management of CKD (NICE 2014)

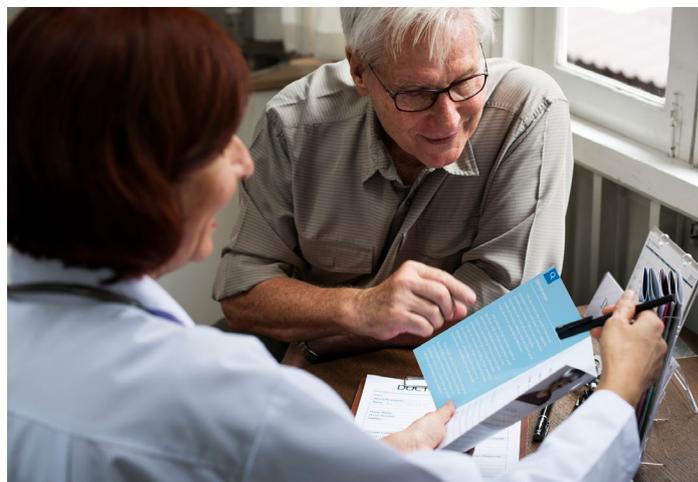


Table 3: Monitoring of Chronic Kidney Disease (NICE Pathways, updated July 2019)

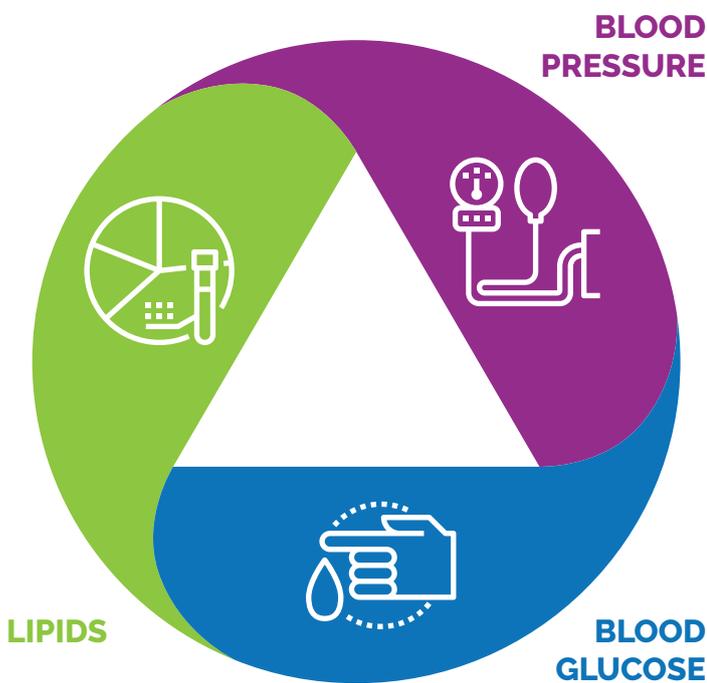
Frequency of monitoring of GFR (number of times per year, by GFR and ACR category) for people with, or at risk of, CKD					
		ACR categories (mg/mmol)			Increasing risk ↓
		Description and range			
		A1 <3 Normal to mildly increased	A2 3-30 Moderately increased	A3 >30 Severely increased	
GFR categories (mL/min/1.72 m ²) Description and range	G1 ≥90 Normal or high	≤1	1	≥1	
	G2 60-89 Mild reduction related to normal range for a young adult	≤1	1	≥1	
	G3a 45- 59 Mildly to moderate reduction	1	1	2	
	G3b Moderate to severe reduction	≤2	2	≥2	
	G4 15-29	2	2	3	

<https://pathways.nice.org.uk/pathways/chronic-kidney-disease>

CKD PROGRESSION DELAY IN DIABETES

The United Kingdom Prospective Diabetes Study (UKPDS), The Diabetes Control and Complications Study (DCCT), and the Epidemiology of Diabetes Interventions and Complications (EDIC) studies demonstrated that effective glycaemic control particularly in the first decade of a diagnosis of diabetes can delay the onset of diabetes complications including diabetic nephropathy (Stratton et al, 2000, Nathan et al, 1993, DCCT/EDIC Study Group 2016).

There are three key components relating to this:



Clinical targets need to be aligned to the individual taking into account other co-morbidities including frailty. In individuals with diabetes and CKD recommended clinical targets are:

- HbA1c <48-53 mmol/mol unless dialysis then 58-68 mmol/mol (JBDS 2016)
- Blood pressure 130/70mmHg
- Total Cholesterol < 4.0mmol/L and LDL < 2.0mmol/L (Atorvastatin – first line) (Joint British Diabetes Society and Renal Association 2018)

Hypertension

Effective blood pressure control improves prognosis in diabetic kidney disease and reduces the risk of increasing albuminuria (Marshall and Flyvbjerg cited in Holt et al (2017; Ch.39). All people living with diabetes should be treated to achieve a blood pressure target 140/90 with a combination of lifestyle intervention and drug therapy. Although this target is lowered to 130/80 in people with diabetes and CKD. In people with type 2 diabetes a seated and standing BP should be taken determine if there is postural hypertension. In nearly all cases, the first-line antihypertensive drug treatment should be an ACE inhibitor or angiotensin receptor blocker (ARB), however the use of multiple antihypertensive agents is often required (NICE 2019).



Lipids

Statins should be considered in any individual with any degree of diabetic nephropathy. The use of Atorvastatin demonstrated a reduced rate of decline in eGFR in the Collaborative Atorvastatin Diabetes Study (Jun M. et al 2014) and is recommended as first line treatment (Mark P.B. et al 2017).



THE IMPACT OF CKD ON THE PRESCRIBING OF MEDICATIONS FOR DIABETES

Insulin

Insulin requirements in individuals with type 2 diabetes and diabetic nephropathy may increase in the early stages of CKD as a result of insulin resistance. In contrast, as renal function deteriorates further and because the kidney excretes insulin, the doses of insulin may need to be reduced to minimise the risk of hypoglycaemia; this is because insulin has a longer profile when CKD slows down excretion. In people using insulin therapy with CKD 3b or below and where the HbA1c is ≤ 58 mmol/mol or below, consider reducing the dose (Winocour et al 2018).



Non-insulin therapies

There is an extensive choice of glucose lowering therapies licensed for the management of type 2 diabetes. Each drug includes in their information packs a summary of product characteristics (SmPC). The dosage of some oral therapies may need to be reduced or discontinued as renal function deteriorates. Some drugs are not licensed for use depending on the stage of renal function. Medications such as sulphonylurea agents are excreted by the kidney and so need to be used in caution in those with CKD 4 and 5 (James J, Gregory R 2018).

For more specific information and tables on individual diabetes therapies for use in people with CKD please visit tiny.cc/TREND-renal

Metformin

Metformin is the first line treatment in the management of type 2 diabetes. The doses may need reducing if the eGFR falls to 45 mL/min/1.73^2 and the drug should be discontinued if the eGFR falls to 30 mL/min/1.73^2 or below due to the risk of lactic acidosis although the risk of this happening is low. There is little impact on weight with this drug; the risk of hypoglycaemia is low unless combined with insulin or a sulphonylurea.

Sulphonylurea and Meglitinide

Sulphonylureas include Gliclazide, Glipizide, Glimpiride, and Tolbutamide. They work by stimulating the beta cells in the pancreas to produce more insulin. They carry a moderate risk of weight gain and hypoglycaemia; therefore they need to be used in caution in those with deteriorating renal function. Meglitinides such as Repaglinide and Nateglinide are useful in some people in CKD 4 and 5 as their length of action is short and the risk of hypoglycaemia reduced.

Dipeptidyl peptidase-4 inhibitors (DPP-4i)

These are incretin enhancers; they stop natural incretin from being broken down by the DPP-4 enzyme, and therefore stimulate insulin response to glucose and prevent glucagon release after a meal. These include:

- Alogliptin - dose adjust according to the eGFR
- Linagliptin - no dose adjustment required in all stages of CKD
- Saxagliptin - dose adjust according to the eGFR. Not licensed for use in CKD 5/renal replacement therapy
- Sitagliptin - dose adjust according to the eGFR
- Vildagliptin - dose adjust according to the eGFR. Not licensed for use in CKD 5/renal replacement therapy

Some DPP-4 inhibitors are associated with an increased risk of heart failure admissions. Saxagliptin was associated with an increase risk of admissions to hospital with heart failure (Scirica et al 2013).

All in class are considered to be weight neutral and the risk of hypoglycaemia is low unless combined with insulin or a sulphonylurea.



Thiazolidinediones (TZD)

Pioglitazone is the only TZD available in the UK. It should not be used in individuals where there is evidence of previous fracture, bladder cancer, and heart failure or fluid retention. Pioglitazone can lead to weight gain. The risk of hypoglycaemia is low unless combined with insulin or a sulphonylurea. Pioglitazone should not be used if eGFR < 15 mL/min/1.73 m²

Sodium Glucose co-Transporter 2 inhibitors (SGLT2i)

SGLT2 inhibitors are a relatively recent addition to the choice of oral glucose-lowering medications. They work by inhibiting the reabsorption of glucose from the proximal tubule in the kidney and thus allowing the loss of glucose (and calories) in the urine. They can lower blood glucose levels and may also produce weight loss.

Drugs in the class include:

- Canagliflozin
- Dapagliflozin
- Empagliflozin
- Ertugliflozin.

Some cardiovascular outcomes trials demonstrate a positive effect on cardiovascular risk in some of these drugs. SGLT2i's have shown positive renal benefits in lowering the rate of albuminuria progression and in reducing worsening of nephropathy (Ali et al 2019).

Use with diuretics

All SGLT2i drugs apart from Canagliflozin can be used with caution with loop diuretics. Advise halving the dose of loop diuretic when starting SGLT2i (Ali et al 2019).

Caution with the use of SGLT2i's

Diabetic ketoacidosis (DKA)

There has been a small number of reports relating to the development of DKA in individuals with type 1 diabetes and also those with type 2 diabetes. The blood glucose level may be relatively low: no higher than 15 mmol/L. These cases seem to be related to the use of SGLT2 inhibitors in people who either have type 1 diabetes, late onset type 1 diabetes, Latent Autoimmune Diabetes in Adults (LADA), or, who have type 2 diabetes and are insulin depleted and/or nutrition depleted people (Department of Health 2016).

Table 4: Risk factors for diabetic ketoacidosis and SGLT2i use (DOH 2016)

 A low beta cell function reserve (e.g., individuals with type 2 diabetes who have low C-peptide levels, Latent Autoimmune Diabetes in Adults (LADA), or a history of pancreatitis)
 Conditions leading to restricted food intake or severe dehydration
 Sudden reduction in insulin doses
 Increased insulin requirements due to acute illness
 Surgery
 Alcohol abuse

Foot amputation risk

The risk of amputation when using SGLT2is was first recognised in 2017 in the CANVAS Study into the use of Canagliflozin (Neal et al 2017). The Department of Health issued advice that included the need to discuss risks in people on **any** SGLT2i. Subsequently the CREDENCE Study (2019) reviewing cardiovascular and renal events in 4401 people taking Canagliflozin found no increased risk of amputation in their study. Advice on risk however should still be included in the consultation when commencing **any** SGLT2i. Department of Health 2017).

When treating individuals who are taking an SGLT-2 inhibitor

- Always test for ketones in any person who is unwell
- Discuss the risk factors for DKA with individuals
- Discuss the signs and symptoms of diabetic ketoacidosis (DKA) and advise users to seek immediate medical advice if they develop any of these
- Discontinue treatment with the SGLT2 inhibitor immediately if DKA is suspected or diagnosed
- Do not restart treatment with any SGLT2 inhibitor in individuals who experienced DKA during use, unless another cause for DKA was identified and resolved
- Interrupt treatment with the SGLT2 inhibitor in individuals who are hospitalised for major surgery or acute serious illnesses; treatment may be restarted once the individual's condition has stabilised
- Discuss the risk of foot ulceration with the individual
- Teach foot examination and provide written information
- Report suspected side effects to SGLT2 inhibitors or any other medicines on a Yellow Card

GLP-1 Receptor agonists

GLP-1 Receptor agonists are non insulin injectable blood glucose lowering therapies used in overweight people with type 2 diabetes; they mimic the action of a gut hormone (incretin) and can lower blood glucose levels and may produce weight loss. These therapies are injected to stimulate insulin response to glucose and prevent glucagon release after meals in people with diabetes. They comprise of four main actions and these include:

- Enhanced insulin production in the presence of food
- Reduced glucagon release from liver to prevent new glucose production (gluconeogenesis)
- Induced satiety so appetite reduced
- The slowing of gastric emptying to reduce post prandial rise in blood glucose level

These actions can lead to reduction in HbA1c with a low risk of hypoglycaemia (unless used with sulphonylureas and/or insulin) and can promote weight loss. GLP-1 injections can be used to improve glucose control in adults with type 2 diabetes by reducing fasting and post prandial glucose levels. They can be used with Metformin, a sulphonylurea or both.

At the time of writing, in the UK three of the available GLP-1 RAs can be used down to an eGFR of 15 mL/min/1.73m². These are:

- Dulaglutide once-weekly
- Liraglutide once-daily
- Semaglutide once-weekly

Additionally, Lixisenatide once-daily and Exenatide once-daily (Byetta) can be used down to an eGFR of 30 mL/min/1.73m², although Exenatide once-daily must be used with caution below an eGFR of 50 mL/min/1.73m². Exenatide once-weekly (Bydureon) should not be used below an eGFR of 50 mL/min/1.73m².

The ADA/EASD guidance provides clear recommendations on treatment pathways for people in CKD and these must be aligned to the individual (Davies et al 2018).

For specific information on medications see tiny.cc/TREND-renal

The Department of Health have issued a warning about the use of GLP-1 Receptor agonists used concurrent use of insulin and the risk of DKA. Cases identified seem to occur when insulin is either abruptly discontinued or dose reduced. Any reduction in insulin dose in people using a GLP-1 RA should be done cautiously (DH (2019).

When to refer to specialist service (NICE CG 182, 2014)

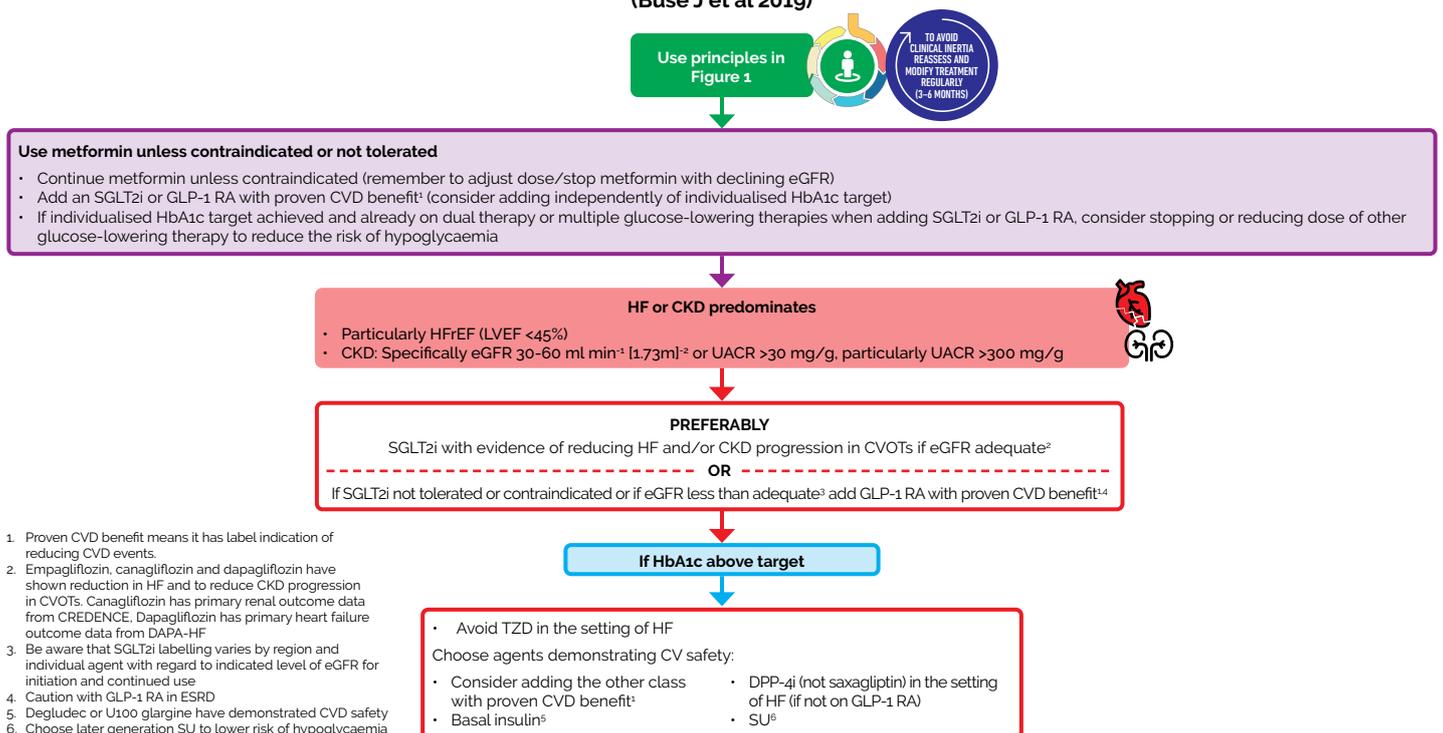
Referral to specialist services in secondary care depends on the eGFR and the ACR. People in the following groups should normally be referred for specialist assessment:

- GFR less than 30 mL/min/1.73 m² (GFR category G4 or G5), with diabetes
- ACR 70 mg/mmol or more, unless known to be caused by diabetes and already appropriately treated
- Hypertension that remains poorly controlled despite the use of at least 4 antihypertensive drugs at therapeutic doses (NICE guideline CG127)
- Known or suspected rare or genetic causes of CKD
- In people where there is a rapid decline in eGFR

⚠ In the UK, SGLT2is can only be initiated above an eGFR of 60 mL/min/1.73m². For other medications please consult the individual SmPCs.

⚠ All products referenced are licensed for insufficiently controlled type 2 diabetes and /or improvement of glycaemic control in type 2 diabetes

CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH INDICATORS OF HIGH-RISK OR ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD), CHRONIC KIDNEY DISEASE (CKD) OR HEART FAILURE (HF) (Buse J et al 2019)



CARE OF PEOPLE WITH DIABETES AND RENAL REPLACEMENT THERAPY

HCPs providing care for people on renal replacement therapy experience significant challenges (Joint British Diabetes Societies and the Renal Association 2017) . These include:

- Anaemia from CKD causes overestimation of HbA1c due to poor red cell turnover. Capillary blood glucose testing tends to be more accurate as renal function worsens
- Increased hypoglycaemia risk as they may experience poor appetite and access to food/snacks on dialysis days
- Fluid restrictions
- Salt restriction
- Difficulty with the timing of medication
- The need to reduce insulin doses on dialysis days
- Transportation difficulties as most individuals are conveyed by ambulance services
- Access to diabetes advice – not all haemodialysis units commission this service
- Increased risk of foot ulceration
- Significant and concurrent cardiovascular disease
- Extensive eye disease is present in many people with diabetes and end stage renal failure (Wong et al 2014)



END OF LIFE CARE

Not all people on renal replacement therapy will be eligible for a transplant; it is therefore important that all HCPs are aware of appropriate end of life care guidance (Diabetes UK, 2017).

Diabetes management needs to be carefully considered in people in end stage renal failure who are dying and early discussion with the Diabetes Specialist Team is recommended. Insulin and other non-insulin therapy may need to be significantly reduced or stopped in those with type 2 diabetes.

Insulin needs to be continued in those with type 1 diabetes. HbA1c testing is not required. In people who are insulin treated, capillary testing can be reduced to 1-2 times a day and blood glucose targets should aim to be between 6-15 mmol/L to reduce the risk of hypoglycaemia and symptomatic hyperglycaemia (JBDS and the Renal Association (2017).



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USEFUL RESOURCES:

- **i** Diabetes UK: www.diabetes.org.uk
- **i** TREND-UK: www.trend-uk.org/resources
Leaflets and guidelines: hypoglycaemia, management of illness, steroids, End of Life, insulin safety
- **i** Renal Association: www.renal.org/



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