Chronic Kidney Disease (CKD) Guidelines

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Introduction:

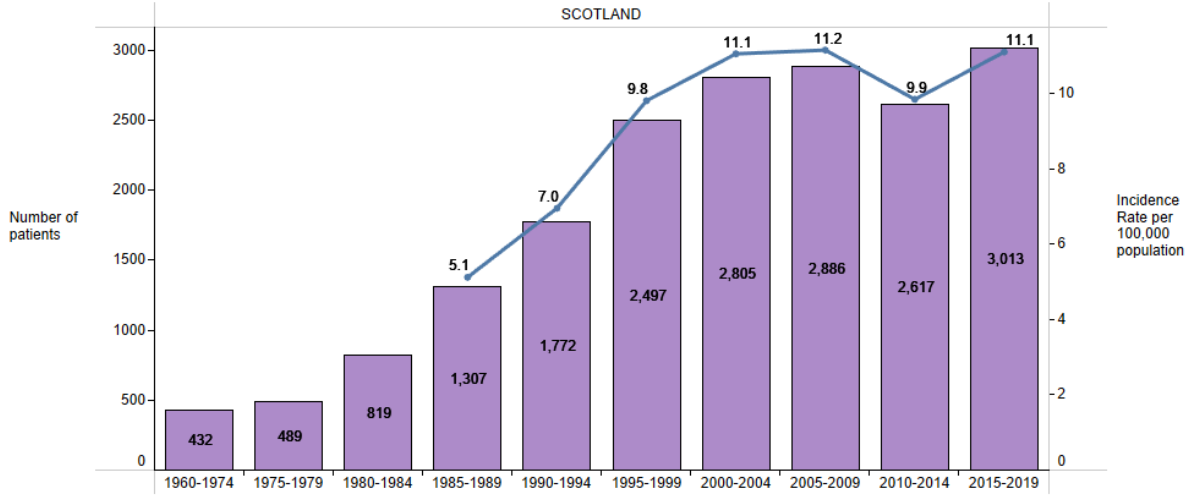
CKD is defined as abnormalities of kidney structure or function present for >3 months with implications for health.[i]

3.19% of the Scottish population were classified as having chronic kidney disease grades 3-5 in 2016[ii] (Grading defined below) which carries with it an increased incidence of vascular disease and a risk of progression to end-stage kidney disease (ESKD). For most patients the risk of vascular disease outweighs the risk of renal progression (<2% of all cases of CKD will progress to ESKD), though the latter is increased with proteinuria and uncontrolled hypertension.

Does diagnosis alter outcome?

One metric of note regarding CKD is that in each decade since the first Scottish patients received kidney replacement therapy (KRT) in 1960 and the first CKD guidance publications in 2002 there was a linear increase in incidence of new patients starting kidney replacement therapy. This has stabilised subsequently. Clearly there are many factors involved but early recognition of disease and management of risk factors is likely to play a significant role in this stabilisation.

Annual Incidence of new patients starting KRT between 1960-2019 in Scotland[iii]



Incidentally 86 patients started RRT in NHS D&G 2015-2019, (11.5 per 100,000 population per year).

Classification of Chronic Kidney Disease

CKD is classified by factors influencing prognosis:

(1) cause of CKD; for example CKD at any given grade due to Diabetic Nephropathy has a worse prognosis than CKD at the same grade due to a previous nephrectomy.

(2) GFR category; This is done by estimating GFR from a patient's serum creatinine, age, gender and race using the Modification of Diet in Renal Disease (MDRD) equation.

(3) albuminuria category; A1 to A3 as per the chart below.

(4) other risk factors and comorbid conditions. These include: age, sex, race/ethnicity, elevated blood pressure (BP), hyperglycaemia, dyslipidemia, smoking, obesity, history of cardiovascular disease, exposure to nephrotoxic agents, malabsorption, dehydrating illness, etc,.

Classification of chronic kidney disease (CKD)[iv]

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min per 1.73 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			

Green: low risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high risk; red, very high risk.

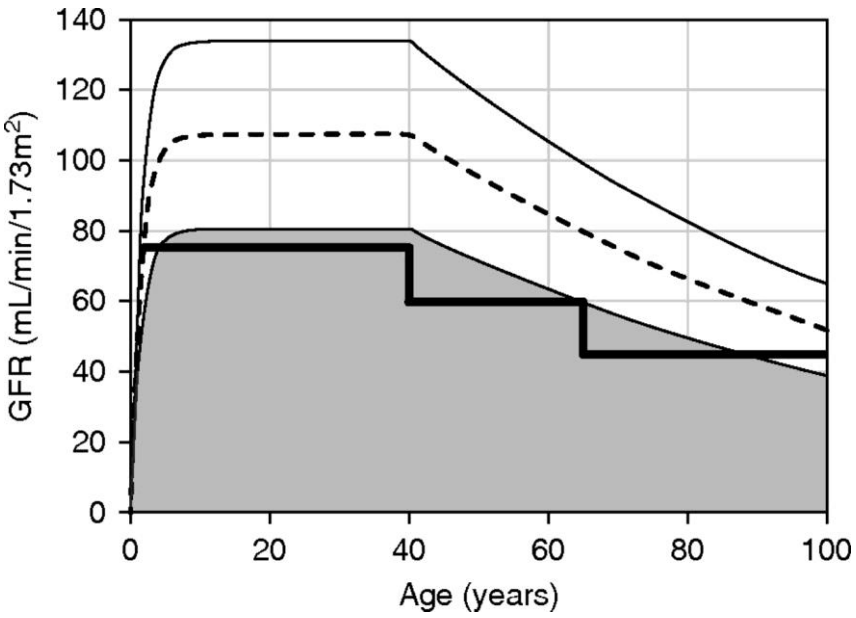
Thus a typical patient may have a diagnosis of "CKD G3b A2 due to probable diabetic nephropathy and hypertension" indicating an eGFR 30-44, Microalbuminuria (uACR 3-30mg/mmol) and history of diabetes and hypertension with no other obvious causes for kidney disease. "Probable" indicates that this is the most likely cause considering the patient, their history and investigations but not including a kidney biopsy. From the chart above this places them in the red/very high risk for progression category: risk factors should be managed and referral considered.

Estimated GFR (eGFR) and its limitations

All U&E reports in patients aged 18-years or over are issued with an eGFR. An advantage of this test is that it does not require a measurement of body weight. Limitations are as follows:

- eGFR is likely to be less accurate at extremes of body type eg malnourished, amputees (overestimates kidney function) and those with high muscle mass or the morbidly obese (underestimates kidney function).
- eGFR underestimates normal or near normal renal function. For this reason the laboratory does not report exact eGFR values > 60 ml/min.
- eGFR overestimates renal function in patients with advanced kidney disease particularly if they are underweight (when we may estimate creatinine clearance using the Cockcroft Gault equation which is based on age, gender, race, serum creatinine and body weight).
- eGFR is not valid for under 18s or if the serum creatinine level is rapidly changing (over days - eg. AKI, patients given Trimethoprim in preceding 2 weeks). For more information on AKI and its investigation / management see https://www.thinkkidneys.nhs.uk/aki/resources/primary-care/.
- Small fluctuations in eGFR are common and do not necessarily indicate progression. While a change from 61 to 59 indicates a change in CKD Grade from G2 to G3a, on its own it has minimal clinical relevance and should not be used alone to instigate referral or further investigation.
- While it is easy to assume changes in eGFR will be progressive and linear, for many patients this is not the case and progression will be non-linear.

As we age our GFR will slowly fall, which is a normal physiological phenomenon. It is not unusual to have an eGFR <60 in patients over 70-years old which is normal. We would therefore advise NOT classifying patients as CKD if they have eGFR 45-60 but no proteinuria, structural abnormality or hypertension.[v]



Age-specific thresholds in relation to age-specific GFR percentiles. The bold line represents an age-adapted threshold for CKD: 75 ml/min per 1.73 m^2 for age below 40-years, 60 ml/min per 1.73 m^2 for age between 40- and 65-years, and 45 ml/min per 1.73 m^2 for age above 65-years. The dashed line represents the median (50th percentile) and the thin solid lines represent the 97.5th and 2.5th

percentiles. The shaded zone is considered as below the normal reference intervals for GFR (<2.5th percentile).[vi]

Monitoring Recommendations:

Recommended Frequency of monitoring is determined by risk of progression:

Legend: GFR and albuminuria grid reflects the risk for progression by intensity of coloring. The numbers in the boxes are a guide to the frequency of monitoring (number of times per year).

GFR categories (ml/min/1.73 m²), description and range	ACR categories (mg/mmol), description and range		
	A1 <3 Normal to mildly increased	A2 3–30 Moderately increased	A3 >30 Severely increased
G1 ≥90 Normal and high	≤1	1	≥1
G2 60–89 Mild reduction related to normal range for a young adult	≤1	1	≥1
G3a 45–59 Mild–moderate reduction	1	1	2
G3b 30–44 Moderate–severe reduction	≤2	2	≥2
G4 15–29 Severe reduction	2	2	3
G5 <15 Kidney failure	4	≥4	≥4

Increased risk

Increased risk

Microalbuminuria and proteinuria:

Microalbuminuria and proteinuria predict progressive renal failure and also amplify the risk of vascular disease. Measurement of 24 hour urine collections are no longer recommended for quantifying urine protein. We now recommend that you request an albumin:creatinine ratio on an untimed specimen of urine, when you want to screen a person with diabetes, hypertension, vascular

disease or chronic kidney disease for microalbuminuria. Please send 10-20 ml of urine in a white topped universal container. Either the first morning urine or a subsequent day time void will do.

Normal albuminuria: Most of us pass a small amount of albumin in our urine. The normal range is 0-3 mg albumin per mmol creatinine, which is roughly equivalent to an albumin excretion rate of less than 30 mg/24 hours on a 24 hour urine collection. No further action is required.

Microalbuminuria: is defined as an albumin:creatinine ratio (ACR)of 3-30 mg/mmol creatinine which is roughly equivalent to an albumin excretion rate of 30 to 300 mg/24 hours in a 24 hour urine collection. You should repeat at least once to confirm.

Proteinuria: uACR >30 mg/mmol creatinine indicates proteinuria and if detected, the lab will report the protein:creatinine ratio (PCR - which assesses all proteins not just albumin) instead of ACR. Proteinuria is best assessed by a protein:creatinine ratio and is defined by ACR>30 / PCR > 50 mg/mmol. Biochemistry will automatically measure and report PCR if the ACR is > 30. Generally we class PCR 50-100 as low level, 100-300 as sub nephrotic and >300 as Nephrotic range proteinuria.

Kidney imaging:

NICE 2015 suggest we offer a renal ultrasound scan to all people with CKD who:

- have accelerated progression of CKD.
- have visible or persistent invisible haematuria.
- have symptoms of urinary tract obstruction.
- have a family history of polycystic kidney disease and are aged over 20 years.
- have a GFR of less than 30 ml/min/1.73 m^2 (GFR category G4 or G5).
- are considered by a nephrologist to require a renal biopsy.

Kidney lesions detected on US/CT that may require further investigation for possible **malignancy** and **obstruction** in the urinary tract are referred to & managed by **Urologists** rather than the renal team.

Referral to Nephrologist:

NICE 2008 + 2014 Guidance recommends the following as referral criteria:

Take into account the individual's wishes and comorbidities when considering referral.

People with CKD in the following groups should normally be referred for specialist assessment:

- GFR less than 30 ml/min/1.73 m^2 (CKD G4 or G5), with or without diabetes.
- uPCR 100 mg/mmol or more, unless known to be caused by diabetes and already appropriately treated.
- uACR 30 mg/mmol or more (ACR category A3), together with haematuria.

- sustained decrease in GFR of 25% or more, and a change in GFR category or sustained decrease in GFR of 15 ml/min/1.73 m^2 or more within 12 months.
- Hypertension that remains poorly controlled despite the use of at least 4 antihypertensive drugs at therapeutic doses.
- Any known or suspected rare or genetic causes of CKD.
- Suspected renal artery stenosis (suspect when: resistant hypertension, >30% eGFR decline with RAASi, asymmetric kidney size on US [1.5cm difference], arteriopath, +/- noncardiogenic pulmonary oedema).

Consider discussing management issues by RMS advice request in cases where it may not be necessary for the person with CKD to be seen directly.

Once a referral has been made and a plan jointly agreed (between the person with CKD or their carer and the healthcare professionals), it may be possible for routine follow-up to take place at the patient's GP surgery rather than in a specialist clinic. If this is the case, criteria for future referral or re-referral should be specified.

Patients over 40-years of age with invisible haematuria should first be referred to urologist.

People with CKD and renal mass or outflow obstruction should normally be referred to urological services, unless urgent medical intervention is required – for example, for the treatment of hyperkalaemia, severe uraemia, acidosis or fluid overload.

Patients with malignant hypertension (BP >180/120) or life-threatening hyperkalaemia (>= 6.5mmol/L) should be admitted urgently to medical receiving).

Managing risk factors in the primary care:

Measures to reduce risk of CVD and progression of renal failure in patients with CKD 3 (added value of nephrology referral likely to be low)

• Target BP <140/90 (no proteinuria), <130/80 (Proteinuria). KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease provides more detailed hypertension advice in these patients.

• ACEi or ARB in patients with diabetes and urine ACR>3, and for all patients with ACR>30 ~PCR>50.

• Assess cardiovascular risk +/- Add a Statin.

• Lifestyle advice: stop smoking, increase exercise, weight management, salt reduction, healthy diet rich in fruit and vegetables (unless hyperkalaemia).

• immunise against influenza and pneumococcus.

Complications you will likely want specialist advice for:

Treatment of complications of renal failure in patients with CKD 4-5 (added value of nephrologist likely to be high). Text in grey for information only – we are not expecting these to be managed in primary care.

- Anaemia – consider oral or IV iron / Erythropoeitin if Hb < 110 for patients with eGFR<35 and other causes excluded. Patients with CKD may have normal MCV and Ferritin levels in spite of iron deficiency. We monitor Iron studies and usually give IV iron for CKD4+ when Hb <110 & TIBC saturation <25%. Erythropoitin treatment is initiated and supplied via renal unit.

- Bone disease – monitor calcium, phosphate, PTH +/- vitamin D and consider vitamin D3, alfacalcidol and phosphate binders if clinically indicated. CKD-MBD is a risk factor for accelerated vascular calcification and atherosclerosis.

- Correction of acidosis by increasing fruit and veg intake (CKD2-3b) or sodium bicarbonate (CKD3b+) if clinically indicated.

- Nutritional assessment by renal dietitian - renal patients are often malnourished and are at increased risk of hyperkalaemia and hyperphosphataemia.

- Advice on hyperkalaemia when serum K persistently > 6 mmol/l – stop relevant drugs, review diet.

Renin Angiotensin System Blockade:

Indications for use in renal disease:

ACEi and ARBs have antihypertensive and antiproteinuric properties that make them drugs of first choice in CKD with urine PCR > 100 mg/mmol (estimated protein output > 1 g/24 hours) and in diabetes with microalbuminuria (urine albumin:creatinine ratio 3-30 mg/mmol). There is no pressing reason to use these drugs as first choice in patients with lesser degrees of proteinuria.

Which drug?

We believe that the benefits of ACEi and ARBs are likely to be class effects so that the choice of agent may be reasonably decided by convenience and cost. ARBs appear to share most of the benefits of ACEi on the kidneys and are particularly indicated with ACE cough or angiooedema. Use of Dual ACEi & ARB or use of ACEi or ARB with a direct renin antagonist is potentially harmful and we do not recommend that this is now used. Where patients have tolerated these combinations for many years without incident we will generally not stop them.

Risks of Renin Aldosterone Angiotensin System Blockade:

Both ACEi and ARBs may cause hyperkalaemia and deterioration of renal function. A small rise in serum creatinine is a normal haemodynamic response to RAS blockade and is not a reason to stop these drugs. As a general rule we will accept a rise in creatinine of up to 30% or a fall in eGFR of up to 20% from baseline provided the final creatinine is less than 300 µmol/l and the final eGFR is > 20 ml/min. Patients whose serum creatinine is going to increase (or eGFR decrease) by more than these values will usually declare themselves within a month of introducing the drug or increasing the dose. Important causes of an exaggerated rise in creatinine (fall in GFR) are:

- excessive hypotension usually <110mmHg systolic.
- volume depletion eg vomiting or diarrhoea.
- co-prescription of a non steroidal anti-inflammatory drug.
- bilateral renovascular disease or hypertensive nephrosclerosis (which is best thought of as a form of intrarenal artery stenosis).

RAAS blockade and renovascular disease:

The incidence of correctable renovascular disease is extremely small though this diagnosis should be considered in middle aged or elderly patients with vascular disease at other sites whose serum creatinine increases by more than 30% (or GFR falls by more than 20%) within one month of RAS blockade. These patients may have inequality of renal size on renal ultrasound (usually more than 1.5cm difference). In the absence of any other obvious cause for deteriorating renal function referral to the renal team for further assessment may be appropriate.

RAAS blockade and pregnancy/breastfeeding:

These medications are contraindicated in pregnancy. They may adversely affect fetal and neonatal blood pressure control and renal function; neonatal skull defects and oligohydramnios have also been reported. They should be discontinued as soon as a patient learns they are pregnant. Nifedipine, Amlodipine, Labetalol and Methyldopa are all options in managing patients pre-existing hypertension and pregnancy. Further information on CKD and Pregnancy available here.[vii]

Monitoring:

The NICE guideline on CKD recommends measurement of serum potassium, urea and creatinine before starting ACEi/ARB therapy, also that these measurements are repeated between one and two weeks after starting treatment and after each dose increase.

Intercurrent vomiting and diarrhoea:

All patients with renal impairment on RAS blockade should be advised to follow NHS Scotland Sick-day-rules guidance. Patients prescribed these medications in the kidney clinic are generally provided with a card to prompt them to follow this. If they develop vomiting or diarrhoea for any reason, as acute kidney injury may occur. It is usually sufficient to stop the ACEi or ARB (along with other medications with potential to cause harm during an AKI/dehydration episode eg. diuretics, Metformin, SGLT2i) temporarily and restart when symptoms have resolved. [viii]

Hyperkalaemia:

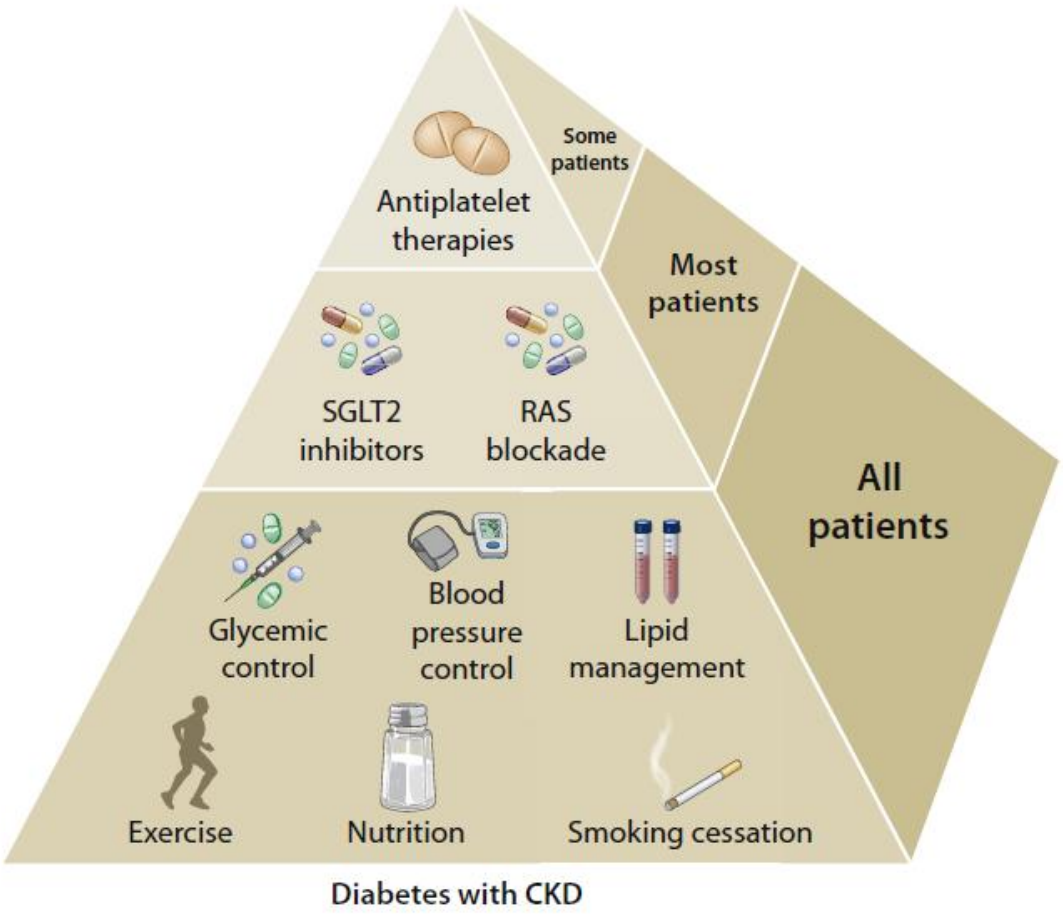
Serum potassium commonly increases by 0.5 mmol/l during ACE inhibitor or ARB treatment. The NICE guideline on CKD recommends that ACEi/ARB therapy should not normally be started if the pre-treatment serum potassium is > 5.0 mmol/l, also that ACEi/ARB therapy should be stopped if serum potassium concentration rises over 6.0 mmol/l. Any serum potassium level above the upper limit of the normal reference range ie > 5.0 mmol/l should prompt a review of diet and drugs, particularly non steroidal anti-inflammatory drugs, potassium supplements and aldosterone antagonists such as spironolactone.

Novel potassium binders (Partiromer & Lokelma) have recently come to the market with the goal of enabling more patients to be able to tolerate their RAAS blockade medication, for example patients with heart failure. While they do lower potassium levels, more significant outcome data are lacking and these drugs were not recommended for use by the SMC. They may be prescribed for a selected number of patients in the renal clinic on an IPTR/selected business case basis.

Patients with diabetes:

We have recently had an updated KDIGO 2020 guideline published on the management of Diabetes in CKD:

- Glycemic control is based on insulin for type 1 diabetes and a combination of metformin and Sodium-GLucose coTransporter-2 Inhibitors (SGLT2i) for type 2 diabetes, when eGFR is >30 ml/min per 1.73 m2 targeting HbA1c individualised for risk factors (below) including hypoglycaemia prevention.
- SGLT2i are recommended for patients with type 2 diabetes and chronic kidney disease (CKD).
- Renin–angiotensin system (RAS) inhibition is recommended for patients with albuminuria and hypertension.
- Aspirin generally should be used lifelong for secondary prevention among those with established cardiovascular disease and may be considered for primary prevention among high-risk individuals, with dual antiplatelet therapy used in patients after acute coronary syndrome or percutaneous coronary intervention.
- Metformin should be first line pharmacological treatment for Type 2 diabetes and can be continued at standard dose down to eGFR 45 then at reduced dose down to eGFR 30. Thankfully metformin associated lactic acidosis is very rare, but when it does occur it has a mortality of 50%. Some patients who are able to follow sick day rules advice may also benefit continuing low dose treatment down to eGFR of 20, but this is not supported by BNF or KDIGO guidance and should be done under specialist supervision.
- SGLT2i Whilst initially devised as a treatment to improve glycaemic control in diabetes, significant improvement in cardiovascular and renal outcomes were noted in the cardiovascular outcome trials conducted to facilitate FDA approval. Since then, further clinical trials have found SGLT2i to be associated with improved renal and cardiovascular outcomes and survival, even in the absence of diabetes. This is an evolving area as more evidence emerges but it is likely that we will see them used in many patients with various causes of CKD and many/most patients with type 2 diabetes. Currently we are avoiding them in patients with a history of PVD or foot ulcers (excess toe amputations in CANVAS trial) and also in patients who have a long duration of insulin treatment (higher incidence of ketoacidosis). Patients on these drugs must be able to follow sick-day guidance and omit them if acutely unwell or fasting.



Figure| Kidney–heart risk factor management (Adapted)

2.2 Glycemic targets

Recommendation 2.2.1: We recommend an individualized HbA1c target ranging from <6.5% to <8.0% in patients with diabetes and CKD not treated with dialysis (Figure 9) *(1C)*.

< 6.5%	HbA1c	< 8.0%
CKD G1	Severity of CKD	CKD G5
Absent/minor	Macrovascular complications	Present/severe
Few	Comorbidities	Many
Long	Life expectancy	Short
Present	Hypoglycemia awareness	Impaired
Available	Resources for hypoglycemia management	Scarce
Low	Propensity of treatment to cause hypoglycemia	High

Figure 9| Factors guiding decisions on individual HbA1c targets. CKD, chronic kidney disease; G1, estimated glomerular filtration rate (eGFR) ≥90 ml/min per 1.73 m^2; G5, eGFR <15 ml/min per 1.73 m^2; HbA1c, glycated hemoglobin.

NB. HbA1c unit conversion 6.5-8.0% = IFCC 48- 64.

Heart Failure:

Kidney and heart failure often coincide; sometimes it is difficult to know which treatment / blood test / symptom to prioritise. If you have a cardiorenal question this national guidance document may be helpful.

Trimethoprim, UTIs and CKD:

Trimethoprim and Cimetidine both block tubular excretion of creatinine and impair potassium excretion. When eGFR is normal this has no consequence. When someone with CKD starts taking Trimethoprim or Cimetidine we expect their creatinine to rise significantly. This rise can persist for as long as 2 weeks. It is not harmful on it's own, but does tend to generate ~10 unnecessary referrals to the renal clinic per year. We are not suggesting that Trimethoprim should not be used for patients. But be aware that it will have an impact upon subsequent creatinine and potassium results.

Nitrofurantoin is ineffective in patients with CKD and is not recommended when eGFR <45 (risk of treatment failure and increased risk of toxicity).

Preparation for end-stage kidney disease and treatment: Kidney care planning:

- It takes time to prepare a patient for kidney failure treatment both physically (treatment of renal complications, assessing fitness for transplantation, assessing potential donors, creation of vascular or peritoneal access) and psychologically. This is another important reason for referring deteriorating CKD3 and all CKD4&5, unless further investigation and management clearly inappropriate.
- We do a lot of this via a dedicated kidney care planning clinic where the nephrologist is supported by a dedicated specialist nurse. End stage kidney failure places significant limitations of a patient's lifestyle as well as life expectancy and the burden of treatment is significant to both the healthcare team and the patient. Prognosis on haemodialysis and fitness for transplantation can be limited by age and comorbidities. 50% of the NHS costs of CKD treatment is spent on <2% of CKD patients who have progressed to end-stage kidney disease. Important decisions about treatment choices; Resuscitation; end-of-life choices and discussions involving the whole family may occur.
- A useful, patient oriented primer on End-stage kidney disease is available on youtube here: Failing kidneys and different treatment options

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Kidney Disease: Improving Global Outcomes (KDIGO):
2020 clinical practice guideline for the management of Diabetes and CKD
2021 for the management of blood pressure in chronic kidney disease