PCDS Wales 2023

Diabetes and the kidneys

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Content

- Epidemiology
- Definition
- Classification
- Treatment options
- Specialist referral
- Primary care & specialist collaboration
- Interpretation of investigations

The vast majority of people with type 2 diabetes and CKD are managed in primary care¹



In its early stages CKD presents with few symptoms, which can make it difficult to diagnose¹

*Stages 3–5 CKD based on NICE CKD guideline referral criteria.

CKD = chronic kidney disease; NICE = National Institute for Health and Care Excellence; T2D = type 2 diabetes.

1. National Chronic Kidney Disease Audit: National Report. Available at: <u>https://www.lshtm.ac.uk/files/ckd_audit_report.pdf</u>. 2. Data on file, AstraZeneca. 3. Hill CJ, *et al. Diabet Med* 2014;31:448–454.

What is chronic kidney disease?

Abnormalities of kidney structure or function, present for >3 months, with implications for health



Kidney disease can significantly impair cardiac function

• Renal and cardiac systems are inextricably linked; acute or chronic disorder of one can induce dysfunction in the other¹



Older patients with CKD are more likely to die from heart disease than advance to end-stage renal disease (ESRD) and require dialysis²

The renal and cardiac systems should not be considered in isolation

Ensure you understand risk of renal decline as early as possible in people with T2D²



Green is representative of low risk, yellow of moderately increased risk, orange of high risk, and red of very high risk.

AKI = acute kidney injury; CKD = chronic kidney disease; CV = cardiovascular; (e)GFR = (estimate) glomerular filtration rate; ESRD = end-stage renal disease; MACE = major adverse cardiovascular events; T2D = type 2 diabetes; uACR = urine albumin; creatinine ratio.

1. NICE clinical guidance. Surveillance report 2017 – Chronic kidney disease. CG157, CG182 and NG8. 2. KDIGO. Kidney Int Suppl (2011) 2013;3:1–150.

Early treatment of declining eGFR in people with CKD is critical to delay kidney failure with or without T2D¹



Adapted from Gansevoort RT, *et al* For illustration purposes only

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; T2D = type 2 diabetes. 1. Gansevoort RT, *et al. J Am Soc Nephrol* 2009;20:465–468

When eGFR is dipping, the clock is ticking

	CV mortality risk ^{1*}		
3a eGFR 45–60 mL/min/1.73m ²	Up to 4.3x greater		
3b eGFR 30–45 mL/min/1.73m ²	Up to 5.2x greater		
4 eGFR 15–30 mL/min/1.73m ² Up to 14x greater			
eGFR <60 mJ /min/1 73 m ² is the single factor associated with the highest risk of MACE and mortality in			

eGFR <60 mL/min/1.73 m² is the single factor associated with the highest risk of MACE and mortality in people with T2D without pre-existing CVD²

1. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int* 2013;3:1–150. 2. Go AS, *et al. BMC Nephrol* 2018;19:146.

^{*}CV mortality risk compared to an eGFR baseline of 90-105 mL/min/1.73m² and an ACR <10. CV mortality ranges: Stage 3a (1.5 to 4.3), Stage 3b (2.2 to 5.2), Stage 4 (4.8 to 14.0) per year;¹ **Accelerated progression defined as eGFR loss >4 mL/min/1.73 m² per year; 36% of patients had T2D at baseline.

ACR = albumin:creatinine ratio; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; MACE = major adverse cardiovascular events; T2D = type 2 diabetes.

Evidence based interventions

- Optimal Glycaemic control
- Optimal Blood pressure control
- ACE inhibitor/ARB
- SGLT2 inhibitors
- Reduce CV risk
- Lipid lowering therapy
- Smoking cessation

Intensive Glycemic Control Slows Progression of Renal Disease in Patients with Type 2 Diabetes



* P<0.05 between groups

UAC = urinary albumin concentration

UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352:837-853.







The Pharmacological Management of Hyperglycaemia in People Living with Type 2 Diabetes and Chronic Kidney Disease

Medscape UK X Guidelines Primary Care Hacks

-

: Dr Kevin Fernando, GP Partner, North Berwick Health Centre; Content Advisor, Medscape Global and UK. Email: kfernando@webm.d.net

Metformin 3 g total maximum 2 g total maximum 1 g total maximum daily dose (in 2–3 daily doses) daily dose (in 2-3 daily dose (in 2-3 daily doses) daily doses) Increased risk of hypoglycaem ia if eGFR < 60. Sulfonylureas Consider reducing cose. Glic azide and gliolizide preferred as metabolised in the liver Repaglinide Acarbose Avoid in those on dialysis Pioglitazone Alogliptin Reduce to 12.5 mg od if CrCl Reduce to 6.25 mg od if CrCl <30 ml/min or <50 ml/min. dialysis required Linagliptin Saxag lipt in Reduce to 2.5 mg od Avoid in those on dialysis Sitagliptin Reduce to 50 mg od Reduce to 25 mg od Vildag lipt in Reduce to 50 mg od if CrCl < 50 ml/min Initiate 100 mg and titrate to 300 mg if 100 mg only Canagliflozin All SGLT2 inhibitors have negligible glucose-lowering effects once eGFR fails below 45. Consider adding an additional glucose-lowering agent if additional glycaemic further glycaemic improvement is required improvement required Certain SGLT2 innio tors have beneficial cardio-renal effects at all stages of renal impairment and should be continued Dapagliflozin Recommended dose is 10 mg See The Mediscape UK Primary Care Hack, Extra-Glycaemic Indications of SGLT2 Inhibitors, for use of SGLT2 inhibitors in this context Empagliflozin Initiate 10 mg and Do not initiate. For For further information, see: titrate to 25 mg if those already taking additional glycaemic emoaglillozin, improvement continue 10 mg only Diabetes Management in Chronic Kidney Disease: A Consensus, Report by the American Diabetes Association and Kidney Disease; required Improving Global Outcomes Initiate 5 mg and titrate to 15 mg if additional glycaemic improvement required. Do not size Report by the American Diabetes Association and the European size Report by the American Diabetes Association and the European Ertugliflozin Association for the Study of Diabetes D ulaglut ide q w Exenatide bid Dose escalation should proceed conservatively i . CrCI30–50 ml/min Exenatide qw Liraglutide od ixisenatide od Semaglutide sc q w Limited experience in patients with severe renal impairment eGFR < 30 Semaglutide oral od Degludec+ Intensify alucose monitoring and dose adjust on an individual basis liraglutide (Xultophy®) Intensify glucose monitoring and dose Glargine + lixisenatide (Suliqua®) adjust on an individual basis All insulins Intensify glucose monitoring and dose adjust on an individual basis due to increased risk of hypoglycaem ia

Blood pressure & Albumin:Creatinine ratio (ACR) NICE guidance 2021

- Diabetes treat BP if > 140/90 mmHg
- ACE-I or ARB are agents of choice

• If ACR is > 30-70 mg/mmol aim BP < 130/80 mmHg on individualized basis (ADA/NICE 2021)

• If ACR is > 3.0 mg/mmol then also use ACE-I or ARB

People with CKD

1.4.27 Offer atorvastatin 20 mg for the primary or secondary prevention of CVD to people with CKD.

- Increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved (see recommendation 1.3.28) and eGFR is 30 ml/min/1.73 m² or more.
- Agree the use of higher doses with a renal specialist if eGFR is less than 30 ml/min/1.73 m². [2014]

See <u>NICE's guideline on chronic kidney disease</u> for CKD classification. People on renal replacement therapy are outside the scope of this guideline.

Oral antiplatelets and anticoagulants for adults

- 1.6.25 Offer antiplatelet medicines to adults with CKD for the secondary prevention of cardiovascular disease, but be aware of the increased risk of bleeding. **[2014]**
- 1.6.26 For guidance on oral anticoagulants for people with CKD, see <u>NICE's guidelines on atrial</u> <u>fibrillation</u> and <u>venous thromboembolic diseases</u>. **[2014, amended 2021]**

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Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.I.
S. Bull, C.P. Cannon, G. Capuano, P.-L. Chu, D. de H. Zhang, B. Zinman, G. Meininger, B.M. Brenne

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D., for the DAPA-CKD Trial Committees and Investigators*

ORIGINAL ARTICLE FREE PREVIEW

Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group*

January 12, 2023 N Engl J Med 2023; 388:1

N Engl J Med 2023; 388:117-127 DOI: 10.1056/NEJMoa2204233

FORXIGA reduces the risk of the primary composite of declining kidney function, ESKD and cardiorenal death¹



ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15 mL/min/1.73 m2 for at least 28 days. Kidney death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason

*The primary composite outcome occurred in 197 patients (9.2%) in the FORXIGA group and in 312 patients (14.5%) in the placebo group

ARR = absolute risk reduction; CI = confidence interval; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; NNT = number needed to treat; RRR = relative risk reduction.

1. Heerspink HJL, et al. N Engl J Med 2020;383:1436-1446.

Invokana + SoC reduces the risk of primary renal composite (ESKD, doubling of serum creatinine, or renal or CV death) vs. placebo + $SoC^{1,2*}$



Intent-to-treat analysis set. SoC: standard of care; ESKD: end-stage kidney disease; CV: cardiovascular; ARR: absolute risk reduction.

1. Invokana 100 mg and 300 mg film-coa

2. Perkovic V, et al. N Engl J Med 2019;380:2295-30

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin in Patients with Chronic Kidney Disease

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Figure 1. Progression of Kidney Disease or Death from Cardiovascular Causes.

Shown are the results of the primary composite outcome of progression of kidney disease or death from cardiovascular causes. Over a median of 2 years of follow-up, progression of kidney disease or death from cardiovascular causes occurred in 432 patients (13.1%) in the empagliflozin group and in 558 patients (16.9%) in the placebo group, representing 42 fewer primary-outcome events per 1000 patients in the empagliflozin group than in the placebo group over 2 years. The inset shows the same data on an enlarged y axis.

- 1.8.17 For adults with type 2 diabetes and CKD who are taking an ARB or an ACE inhibitor (titrated to the highest licensed dose that they can tolerate), offer an SGLT2 inhibitor (in addition to the ARB or ACE inhibitor) if:
 - ACR is over 30 mg/mmol and
 - they meet the criteria in the marketing authorisation (including relevant estimated glomerular filtration rate [eGFR] thresholds).

In November 2021, not all SGLT2 inhibitors were licensed for this indication. See <u>NICE's</u> information on prescribing medicines. [2021]

- 1.8.18 For adults with type 2 diabetes and CKD who are taking an ARB or an ACE inhibitor (titrated to the highest licensed dose that they can tolerate), consider an SGLT2 inhibitor (in addition to the ARB or ACE inhibitor) if:
 - ACR is between 3 and 30 mg/mmol and
 - they meet the criteria in the marketing authorisation (including relevant eGFR thresholds).

In November 2021, not all SGLT2 inhibitors were licensed for this indication. See <u>NICE's</u> information on prescribing medicines. [2021]

Extra-Glycaemic Indications of SGLT2 Inhibitors

Medscape UK \times Guidelines

Primary Care Hacks





Renal and cardiovascular protective drugs

RAASi therapy

SGLT2-inhibitors

Finerenone

Finerenone

- A nonsteroidal, selective antagonist of the mineralocorticoid receptor (MR)
- Aldosterone binds to MR in both epithelial (e.g. kidney) and non-epithelial (e.g. heart, blood vessels) tissues and increases blood pressure through induction of sodium reabsorption and potassium excretion
- Mineralocorticoid receptor over-activation is a major driver of cardiovascular and kidney damage through oxidative stress, inflammation and organ fibrosis
- Unlike the steroidal MRAs spironolactone and eplerenone, finerenone is distributed relatively equally between heart and renal tissue
- Finerenone has been shown to reduce the risk of CKD progression and cardiovascular events in people with T2DM vs. placebo

Does finerenone slow progression of CKD and reduce cardiovascular mortality in patients with type 2 diabetes?



PHASE 3, DOUBLE-BLIND, MULTICENTER, RANDOMIZED, CONTROLLED TRIAL



Reference: Bakris GL, Agarwal R, Anker S, Pitt B, et al. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. NEJM

VA by Dhwanil Patel 🈏 @iheartkidneys

Finerenone for treating CKD in T2DM (NICE TA, 2023)

1 Recommendations

- 1.1 Finerenone is recommended as an option for treating stage 3 and 4 chronic kidney disease (with albuminuria) associated with type 2 diabetes in adults. It is recommended only if:
 - it is an add-on to optimised standard care; this should include, unless they are unsuitable, the highest tolerated licensed doses of:
 - angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) and
 - sodium–glucose cotransporter-2 (SGLT2) inhibitors and
 - the person has an estimated glomerular filtration rate (eGFR) of 25 ml/min/ 1.73 m² or more.

Finerenone in practice

- Formulary status currently "Specialist initiation" or "Hospital only" across Wales
- As familiarity increases, likely to be a transition to primary care
- RAASi therapy, SGLT2-i and finerenone will likely work together for better renal protection than any of them alone
- SGLT2-i may be preferred in hyperkalaemia
- Finerenone may be preferred if risk of DKA or foot disease
- NICE currently places finerenone as an add-on to RAASi and SGLT2-i

When to refer to renal

NICE CKD Guideline

Referral criteria

- 1.5.5 Refer adults with CKD for specialist assessment (taking into account their wishes and comorbidities) if they have any of the following:
 - a 5-year risk of needing renal replacement therapy of greater than 5% (measured using the 4-variable Kidney Failure Risk Equation)
 - an ACR of 70 mg/mmol or more, unless known to be caused by diabetes and already appropriately treated (see recommendations 1.6.6 and 1.6.7)
 - an ACR of more than 30 mg/mmol (ACR category A3), together with haematuria
 - a sustained decrease in eGFR of 25% or more and a change in eGFR category within 12 months
 - a sustained decrease in eGFR of 15 ml/min/1.73 m² or more per year
 - hypertension that remains poorly controlled (above the person's individual target) despite the use of at least 4 antihypertensive medicines at therapeutic doses (see also <u>NICE's guideline on hypertension in adults</u>)

NICE CG 203, 2021

- known or suspected rare or genetic causes of CKD
- suspected renal artery stenosis. [2021]

Kidney Failure Risk Equation (KFRE)

- A person's 5 year risk of needing RRT (dialysis or transplant)
- Not yet operational in Wales and most of England
- Requires LIMS update and switch from MDRD to CKD-EPI eGFR equation

In practice

- Follow NICE Guidance
- Average eGFR for starting dialysis ~7 or 8 ml/min/1.73m²
- Early identification of CKD progression important
- If patient has diabetic neuropathy or retinopathy, diabetes is almost certainly the cause of CKD
- Renal specialists unlikely to manage differently unless sudden onset proteinuria (note gap between ACR tests)
- If in doubt, it's reasonable to ask nephrologist for management advice
- ACR underutilised in primary and secondary care
- Potassium may be a factor for earlier referral
- Discuss CKD 'diagnosis' with patient

eGFR over time



Kidney Function Graph Surveillance alert

GP referral letter

Kidney Function Graph Surveillance (KFGS)



- SWW Renal Service adopted the UK-wide ASSIST-CKD programme
- Aim to identify people with CKD at the greatest risk of disease progression
- Avoid late referral which is associated with a 2-fold increase risk of death
- Minimal impact on workload
- Over 3 million eGFR results imported from GPs across SBU and H Dda
- Review approximately 500 graphs a week
- Over 100,000 graphs have been reviewed to date
- Approx. 5% of the graphs reviewed sent to GPs
- Currently evaluating our KFGS programme

Primary Care Pilot

Cardio-Renal-Diabetes Service

Primary care Cardio-Renal-Diabetes pilot

- A small team of pharmacists and pharmacy technicians working part time
- One GP Cluster in Hywel Dda HB
- Identify people at risk of CKD progression (diabetics and non-diabetics):
 - Check CKD coding
 - -Arrange ACR and eGFR as required
 - Patient education (without causing undue concern)
 - Medication review: start/optimise RAASi, SGLT2-i, finerenone, atorvastatin etc. and stop potentially harmful meds
 - Appropriate monitoring and referral: GPs, specialists, smoking cessation, diet & exercise
- Programme evaluation: interventions, patient and staff surveys, health economy
- Ultimate aim to create a sustainable and scalable primary care CKD service

60-year-old woman

Type 2 Diabetes 8 years. Hypertension & moderate diabetic retinopathy

Treatment Metformin, Linagliptin 5mg, Ramipril 5mg/day, Atorvastatin 20mg

HbA1c	58 mmol/mol
eGFR	56 ml/min/1.73m ²
Albumin creatinine ratio	16 mg/mmol
BP	150/90

The test is repeated 3/12 same results

- 1. What is the diagnosis?
- 2. How do you classify CKD?



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- 1. What is the diagnosis?
- 2. How do you classify CKD?

				Albuminuria stages, description and range		
			Al	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)
range	G1	Normal or high	≥90			
n and n ²)	G2	Mild	60 - 89			
scriptic '1.73 n	G3a	Mild – moderate	45 - 59		******	
ies, de: L/min/	G3b	Moderate – severe	30 - 44			
ategor (m	G4	Severe	15 - 29			
GFR c	G5	Kidney failure	<15			

45 year old man, T2DM 7 years, Previous laser therapy for retinopathy

Treatment Metformin 1g bd, Dapagliflozin 10 mg, Sitagliptin 100mg 5mg, Ramipril 2.5mg, Atorvastatin 10mg

HbA1c	48 mmol/mol
eGFR	70 ml/min/1.73m ²
Albumin creatinine ratio	140 mg/mmol
LDL Cholesterol	3.0 mmol/l
Blood pressure	150/95

- 1. What is the diagnosis?
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- 3. How should we manage him?



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categories (mL/r

GFR

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G1	Normal or high	≥90			
G2	Mild	60 - 89			*****
G3a	Mild – moderate	45 - 59			
G3b	Moderate – severe	30 - 44			
G4	Severe	15 - 29			
G5	Kidney failure	<15			

68 year old man Type 2 Diabetes 15 years, IHD, Hypertension, dyslipidaemia, DM retinopathy, ex-smoker,

Treatment

Metformin 500mg bd, Gliclazide 80mg bd, Linagliptin 5mg Aspirin 75mg, Ramipril 10 mg, Bisoprolol 5mg, Atorvastatin 80mg,

HbA1c	68 mmol/mol
eGFR	28 ml/min/1.73m ²
Albumin creatinine ratio	100 mg/mmol
LDL Cholesterol	1.6 mmol/l
BP	125/75 mmHg
BMI	32

ACR > 30 for 6 years

- 1. What is the diagnosis?
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1	Normal or high	≥90				
2	Mild	60 - 89				
3	Mild – moderate	45 - 59				
3	Moderate – severe	30 - 44				
1	Severe	15 - 29			*****	
5	Kidney failure	<15				

Summary

- Early identification is vital
- Interventions to retard decline of eGFR
- Attenuate cardiovascular risk
- Collaboration between primary care, diabetes and renal teams is important