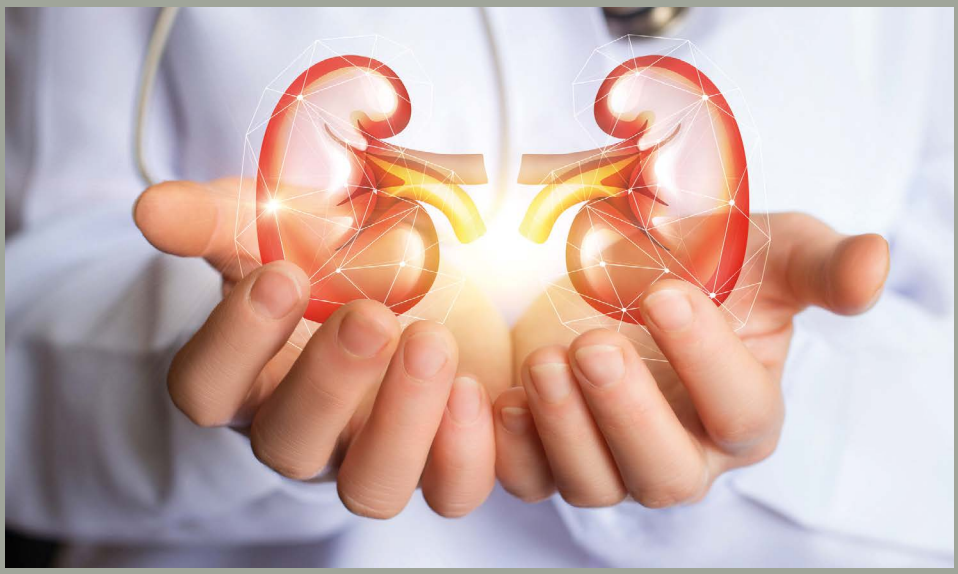
PULSE

HANDBOOK

Redefining the traditional approach to type 2 diabetes care

The cardiorenal benefits of NICE recommended therapies for type 2 diabetes mellitus

Prescribing information can be found at the end of this handbook.



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Foreword

Abbreviations

ACEi	Angiotensin-converting enzyme inhibitor
ACR	Albumin-to-creatinine ratio
ARB	Angiotensin receptor blocker
ASCVD	Atherosclerotic cardiovascular disease
BMI	Body mass index
BP	Blood pressure
CKD	Chronic kidney disease
CVD	Cardiovascular disease
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
ESKD	End-stage kidney disease
HbA1C	Haemoglobin A1C
HDL	High density lipoprotein
HF	Heart failure
hHF	Hospitalisation for heart failure
HR	Hazard ratio
LDL	Low density lipoprotein
LVEF	Left ventricular ejection fraction
MI	myocardial infarction
NICE	National Institute for Health and Care Excellence
QOF	Quality and Outcomes Framework
SGLT2	Sodium-glucose co-transporter 2
SGLT2i	Sodium-glucose co-transporter 2 inhibitor
SRH	Self-reported health
T2D	Type 2 diabetes mellitus
TC	Total cholesterol
TG	Triglycerides

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Background

Chronic Kidney Disease (CKD) is a public health emergency, affecting an estimated 10% of adults in the UK.[1] CKD places people at risk not only for end stage kidney disease (ESKD) requiring dialysis or a transplant, but also for cardiovascular disease (CVD).

Hypertension, obesity, diabetes and CVD are key risk factors for developing CKD and their prevalence is rising, particularly in areas of socioeconomic deprivation.[2] UK Renal Registry data shows that diabetes is the most common identifiable primary renal disease in those starting kidney replacement therapy (31.3%).[3] In addition to the individual and societal economic impacts and the wider physical and mental health impacts for people living with this disease, there will be a significant economic benefit to delaying or avoiding dialysis, given the cost to the NHS of £34,000 per year per patient.[1]

Complicating this further is the evidence of under-diagnosis of CKD in primary care.[4,5] The National CKD Audit in 2017 found that overall, only 70% of patients with CKD were coded or registered as having this diagnosis on their GP record.[6] Those who had CKD but were not coded were at much greater risk of morbidity and mortality.[7] More recently, in 2020–21, only 3.96% of patients across England were coded (registered on their GP record) as having CKD.[8] Added to this, awareness of CKD is often poor. A Kidney Care UK survey of patients highlighted that 6 in 10 of those with diabetes or high blood pressure were not aware that this placed them at increased risk of developing CKD.[9]

How treatment has changed over time

Until recently, treatment for people with CKD and diabetes focused on blood glucose control, and the control of modifiable cardiovascular risk factors such

as hypertension, smoking, weight loss and cholesterol. However, the advent of new specific treatments for CKD represents an exciting opportunity for primary and secondary care to work together with patients to both raise awareness of CKD and reduce the burden of disease.

Sodium-glucose Cotransporter-2 inhibitors (SGLT2i) are drugs that reduce blood sugar levels and can lower the risk of both CKD progression and cardiovascular events. NICE recommends that an SGLT2i be offered to patients with CKD as an add-on to the highest tolerated licensed dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) unless contraindicated and; they meet prespecified eGFR criteria and either have T2D or a urine albumin-to-creatinine ratio of >22.6mg/mmol or more.[10,11] NICE recommends that SGLT2i are considered early (i.e., as soon as metformin tolerability is confirmed, or alone if metformin is contraindicated) for those at high risk of developing CVD[10] – this includes those with a QRISK2 score of >10% in those over 40, the presence of more than one risk factor for CVD in those under 40 (hypertension, dyslipidaemia, smoking, obesity, and family history (in a first-degree relative) of premature CVD).[10] In reality this will represent the majority of people living with diabetes in primary care.

Goals of treatment

Early identification of CKD allows for timely and complete optimisation of medications targeted at both preventing CKD progression and reducing CVD risk. This includes SGLT2i, but also angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB), statins, and finerenone. Under-diagnosis of CKD limits the opportunity to prescribe these medications to those who could benefit.

Providing optimal evidence-based care to all

In this new era of specific, clinically efficacious, and cost-effective therapies for CKD, it is imperative that primary care, community care, and secondary care multi-disciplinary teams work in collaboration with patients and members of the public to identify and deliver the best care to all. Only by doing so will we reduce the significant economic, health and quality of life burden of both CKD and CVD.

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*See page 17

Introduction

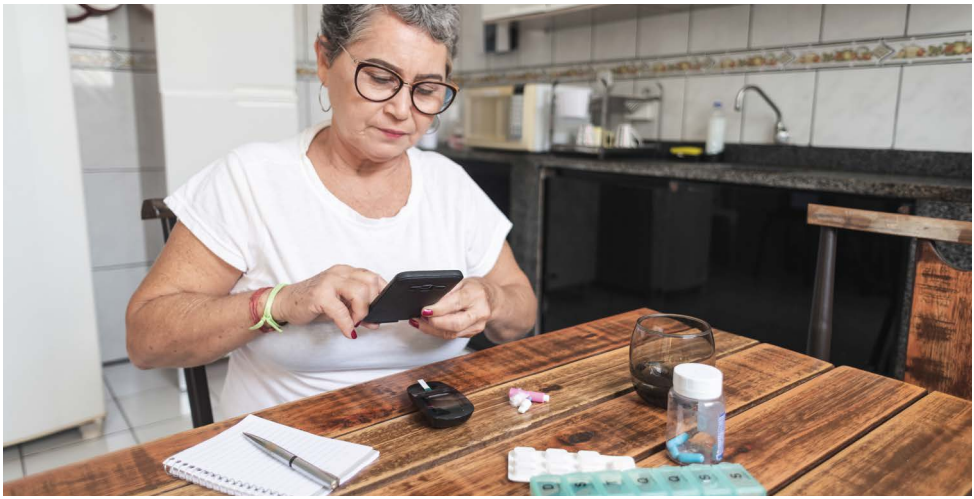
It is estimated that 3.2 million adults in the UK have a confirmed diagnosis of diabetes, with type 2 diabetes mellitus (T2D) accounting for 90% of these cases.[1] Associated complications such as chronic kidney disease (CKD) and heart failure (HF) are increasingly common.[2] Failing kidney health through inter-organ crosstalk[2] can lead to HF (and vice versa), of which around 920,000 people in the UK have a diagnosis.[3] This drives a vicious cycle that results in high symptom burden and mortality risk for patients.[2]

Standard care for T2D patients has previously focused on reducing blood glucose levels; however, guidance has moved beyond sugar and towards a more holistic approach that focuses on reducing the burden of comorbidities.[1]

Some comorbidities, such as CKD, may remain asymptomatic for longer, and therefore require more specific testing strategies to identify patients who may be at risk for renal decline.[4] The role of the primary care practitioner here is vital. The aim of CKD management is to slow disease progression,[5] and as such, early intervention can allow more time for evaluation and treatment.[4]

The National Institute for Health and Care Excellence (NICE) guidance recommends that a sodium-glucose co-transporter 2 inhibitor (SGLT2i) be considered as an add-on treatment for patients prescribed metformin with T2D[1], those with T2D and CKD,[5] and those with T2D at risk for cardiovascular disease (CVD).[1]

SGLT2is have glucose lowering beneficial effects for patients with T2D,[6] but also present an opportunity to improve the cardiorenal health of patients irrespective of diabetes status.[7]



Meet Debbie

This is a fictional patient and does not attest to an individual.

Patient profile

Debbie saw her doctor for her annual diabetic review as she was diagnosed with T2D 3 years ago. She found out that her eGFR has decreased since her last appointment a year ago, from 72ml/min/1.73m^2 to 52ml/min/1.73m^2. Debbie's doctor considers a referral to nephrology because of the decline in renal function.

Debbie's symptoms present as needing to urinate frequently, particularly at night which disturbs her sleep. Debbie also frequently feels very fatigued, which means she struggles to concentrate at work. She is fearful for her future and worries she won't get to see her grandchildren grow up.

Age: 63

Medical conditions:

- T2D
- Hypertension
- Decline in renal function

Clinical results

- Weight 95kg; height 172cm; BMI 32.1 kg/m^2
- eGFR 52ml/min/1.73m^2
- uACR 35mg/mmol
- HbA1c 52mmol/mol
- BP 126/78mmHg
- LVEF ≥50%
- Lipid profile: TC: 194 mg/dl, TG: 194.64, HDL: 39.99, LDL: 101.94

Current medications:

- Ramipril 10mg once daily
- Metformin 500mg twice daily

How can Debbie's GP help?

Why is it important to treat T2D and its associated comorbidities?

Approximately 50% of patients diagnosed with T2D will go on to develop renal diseases, including CKD.[8] Both CKD and diabetes fall under the remit of the general practice Quality and Outcomes Framework, which results in patients with this combination being most likely to be managed in primary care.[9] **One study reports 42.7% of patients being seen only in primary care**, compared with 36% being seen only by diabetologists and 21.6% being seen only by nephrologists.[9] A diagnosis from a primary care practitioner often occurs during later stages of CKD when there are fewer options available to slow down adverse outcomes,[4] and late presentation to specialist renal services is associated with increased morbidity and mortality.[10]

Long-term hyperglycaemia contributes to glomerular and tubular damage[8]

CKD is defined as impaired renal function or elevated urinary albumin excretion, or both[8]

Estimated glomerular filtration rate (eGFR) is measured to assess renal function

Structural damage within the kidneys is measured by testing urine albumin-creatinine ratio (uACR)

Cardiorenal disease is the most common first disease appearance in T2D patients with no previous history of cardiovascular or renal disease at diagnosis.[2]

Impact on mortality

There is a higher risk of death and CVD complications for patients with cardiorenal disease and T2D compared with those with T2D alone.[2] The pathophysiology of CKD and HF are interlinked, with a two-fold increase in the risk of CKD where HF is present and vice versa.[2]

Shared factors that contribute to the development of both CKD and CVD in T2D:[8,11]

- Hypertension
- Hyperglycaemia
- Obesity
- Dyslipidaemia

Classic management of CKD, such as angiotensin receptor blockers (ARBs), used to slow progressive renal decline in T2D do not reduce the prevalence of CKD or its associated mortality.[2]

CKD impacts patients in multiple ways:[5]

- Impact on mental and emotional wellbeing[5]
- Time spent in hospital for dialysis[5]
- Reduced quality of life[5]
- Increased mortality risk[2]

There is an unmet clinical need to take preventive measures to treat CKD in its early stages to delay disease progression, decrease the need for advanced therapies, such as dialysis and transplant, and reduce patient morbidity and mortality.[5]

Economic burden of T2D and CKD

The economic burden of both T2D and CKD are substantial.[12] The cost of care, loss of productivity and impact on patient quality of life all factor into the overall cost to society of these illnesses.[13]

In England alone in 2022/23, diabetes cost the NHS £1.53 billion.[12] 15% of the total spend on prescription items in England in the same period was for drug items used to treat diabetes.[12]

It was estimated that for 2023, treatment of CKD (excluding treatment of end-stage disease) would cost the UK NHS £1.95 billion.[13] The additional cost of treating end-stage disease in 2023 was estimated at a further £1.05 billion for dialysis and £293 million for kidney transplantion.[13] In all cases, these **figures are predicted to increase significantly by 2033**.[13]

- In addition to the cost of treatments for CKD, there is also the burden of lost patient and carer productivity, estimated at **£372 million for 2023**, and predicted to increase in the future.[13]
- Patient health-related quality of life is negatively impacted by CKD-related treatment burden, particularly in those with later stage disease where dialysis is required.[14]

There is a mean healthcare cost of £5401 per patient per year, regardless of CKD stage[15]

Effectively identifying and treating patients with CKD can save the NHS money and resources and improve patient quality of life.[15]

NICE recommendation

In patients with T2D and CKD, NICE recognised the value of using dapagliflozin as an add-on therapy to slow CKD disease progression.[5]

- NICE agreed clinical trial evidence shows add-on therapy is more effective than standard care alone
- This application is noted as being a cost-effective use of NHS resources.[5]

Similarly, The Kidney Disease: Improving Global Outcomes (KDIGO) 2024 guidelines recommend treating adults with T2D and/or CKD with SGLT2is. KDIGO also recognise the benefits SGLT2is represent in terms of reducing the risk of cardiovascular death, myocardial infarction and acute kidney injury.[16]

Despite key guidelines recommending SGLT2i usage in T2D and CKD, a recent study found that only 17% of those indicated for SGLT2i treatment were prescribed them.[17]

NICE guidance for treating T2D

Taking an individualised approach to diabetes care

The current approach recommended by NICE is that the patient preferences and comorbidities should be taken into account.[1] Part of counselling the patient should include identifying what is important to the patient about managing their condition and what they hope to achieve through treatment.[18]

Case study highlight: Debbie's priorities for treatment:

- Being on the correct medication
- Preventing her kidney function from worsening
- Living a longer, healthier life so that she can spend time with her grandchildren
- Better control of breathlessness and fatigue
- Lifestyle advice

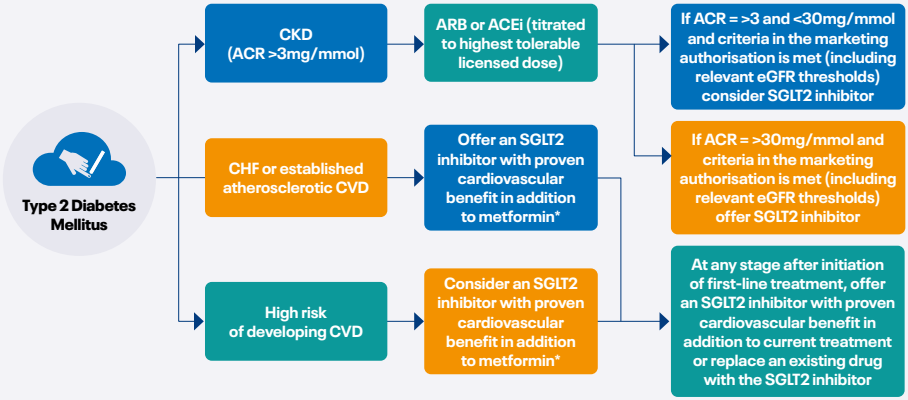
Reviewing the patient's medications

NICE guidance advises that the risk of polypharmacy should be taken into account, and stopping medications that are not effective should be considered.[1]

Case study highlight: There is a valid indication for all of Debbie's medication; however, she needs more help in preventing her renal function from declining further.

Indications for SGLT2i

The NICE guidance for the treatment of T2D



*Where metformin is contraindicated or not tolerated, an SGLT2i with proven cardiovascular benefit can be offered as a first-line monotherapy.

Adapted from: NICE Type 2 Diabetes in Adults: Management (NG28), 2022

NICE guidance for treating CKD with T2D

The standard treatment pathway for adults with CKD includes ACEis or ARBs in conjunction with lifestyle advice, such as dietary interventions, with the goal of slowing disease progression and reducing cardiovascular morbidity and mortality.[5]

The prognosis of CKD can be calculated using eGFR and albuminuria measurements.

KDIGO: Prognosis of CKD by GFR and albuminuria categories

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk. GFR, glomerular filtration rate.

GFR categories (ml/min/1.73m²) Description and range				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	>30 mg/g >3 mg/mmol
	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			
	G3a	Kidney failure	<15			

Adapted from: KDIGO. Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. 2024

Assessment of kidney function should be calculated by measuring urine albumin and GFR.[16]

Serum creatinine: high creatinine levels may indicate CKD[19]

eGFR: calculated using serum creatinine, age and sex. If cystatin C measurements are available, eGFR should be calculated using both creatine and cystatin C measurements.[16] A higher number is better and a value <60mL/min/1.73m^2 may indicate that the kidneys are not working normally, while an eGFR <15mL/min/1.73m^2 indicates kidney failure.[19]

uACR: calculated by dividing urine albumin by urine creatinine. A uACR ≥30mg/g can be a sign of albuminuria[19]

NICE guidance on SGLT2i use[5,20]

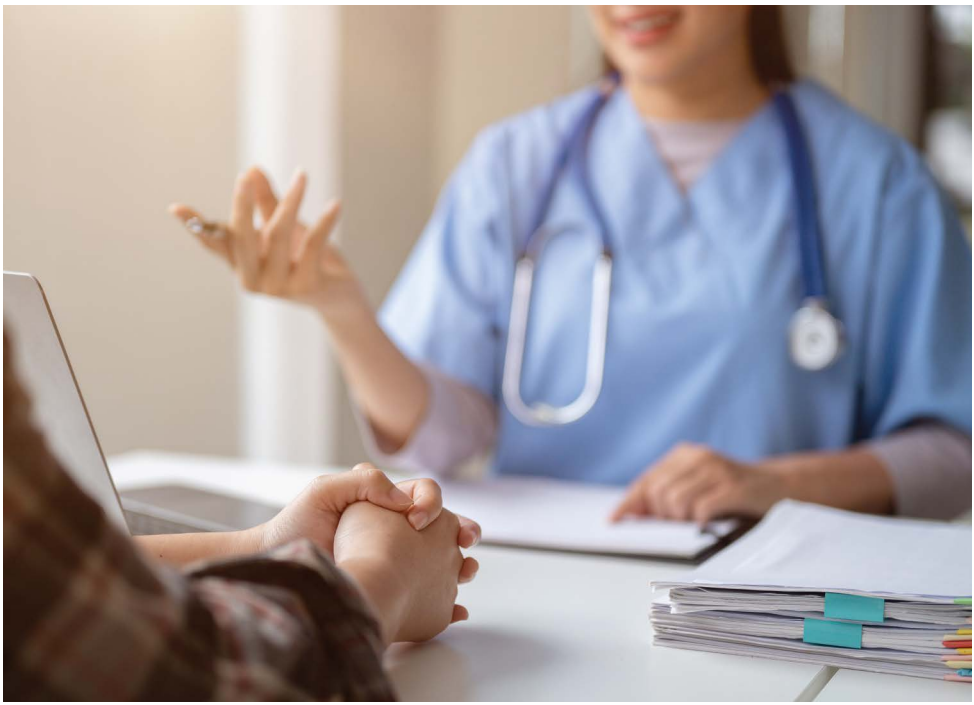
NICE recommends that an SGLT2i be offered to patients with CKD as an add-on to the highest tolerated licensed dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) unless contraindicated **and**;

- they meet prespecified eGFR criteria

and either have

- T2D
- or a urine albumin-to-creatinine ratio of >22.6mg/mmol or more

How would you treat Debbie?



Case study highlight: Owing to her declining renal function, it is decided that Debbie would benefit from an SGLT2i. There are multiple SGLT2i choices available, but their indications must be considered before prescribing. She is also given general lifestyle advice about physical activity and her diet.

The benefits of SGLT2i treatment extend beyond lowering blood glucose levels

The mechanism of action in the kidneys that facilitates lowering glucose levels has several downstream effects, such as natriuresis, vascular compliance and improved endothelial function.[21]

SGLT2i treatment has shown to slow the decline in renal function for patients with CKD due to the lowering of intraglomerular pressure.[22] This stabilisation of renal function presents a valuable treatment option for these patients who previously could only take ACEis to prevent kidney failure.[22]

Debbie's doctor decides to prescribe Forxiga (dapagliflozin)

Because of her concerns about the mortality risk of CKD, Debbie's GP decides to prescribe dapagliflozin as it is the only SGLT2i to have demonstrated mortality benefit versus placebo and on top of standard of care.[22]

Case Study Highlight:
Dapagliflozin is a good choice for this patient because:

- She is already taking metformin and ramipril at optimised doses
- Her eGFR is 52ml/min/1.73m^2
- Her uACR is 35mg/mmol
- The mortality benefits align with her treatment goals of spending more time with her family

Debbie's doctor has explained why dapagliflozin is a good choice for her, how it works, and how it can benefit her. Debbie agrees to begin treatment and will be prescribed one dapagliflozin 10mg tablet daily. Patients with severe hepatic impairment should begin with a dose of 5mg once daily, which can be increased to 10mg if tolerated.[6]

Dapagliflozin is indicated for patients with:

T2D

- In adults and children (≥10 years) for treating insufficiently controlled T2D as an adjunct to diet and exercise
  - As monotherapy if metformin is considered inappropriate due to intolerance
  - In addition to other medicinal products for the treatment of T2D[6]

CKD

- In adults for the treatment of CKD[6]

HF

- In adults for the treatment of symptomatic chronic HF[6]

This short video can help to explain to patients about how dapagliflozin works

Once daily dosing

Starting treatment with dapagliflozin is simple as there is no need for titration. T2D, CKD and HF patients are recommended to take one dapagliflozin 10mg tablet once daily.[6] Patients with severe hepatic impairment should begin with a dose of 5mg once daily, which can be increased to 10mg if tolerated.[6]

Polypharmacy can contribute to a reduction in self-reported health (SRH) by individuals with diabetes.[23] In turn, patients with diabetes and moderate or poor SRH have poorer glycaemic control and higher rates of complications than those with good or excellent SRH.[23]

Diabetes patients may also struggle with adherence to treatment.[24] Studies show that reducing pill burden may improve disease management in patients with poor medication adherence.[25]

Introducing dapagliflozin...

Image not to scale
For illustrative purposes only

Mode of Action
SGLT2 inhibition

Molecule/Generic Name
Dapagliflozin

Indications
- Chronic kidney disease
- Insufficiently controlled Type 2 diabetes
- Symptomatic chronic heart failure

Dosing
- Oral tablet
- 10 mg once daily
- 5 mg if person has severe hepatic impairment

An established treatment with strong supporting data

Extensive data support the benefits of dapagliflozin, with >10 years of real-world data demonstrating safety and efficacy claims.

DAPA-CKD Trial[22]

4304 participants with an eGFR 25-75ml/min/1.73m^2 and a uACR 200-5000 mg/g **received either dapagliflozin 10mg once daily or placebo** on top of standard of care

Dapagliflozin treatment resulted in a **significantly lower rate of death from renal or cardiovascular causes compared to placebo**

The safety profile of dapagliflozin in patients with CKD was consistent with the known profile of dapagliflozin in this clinical trial population

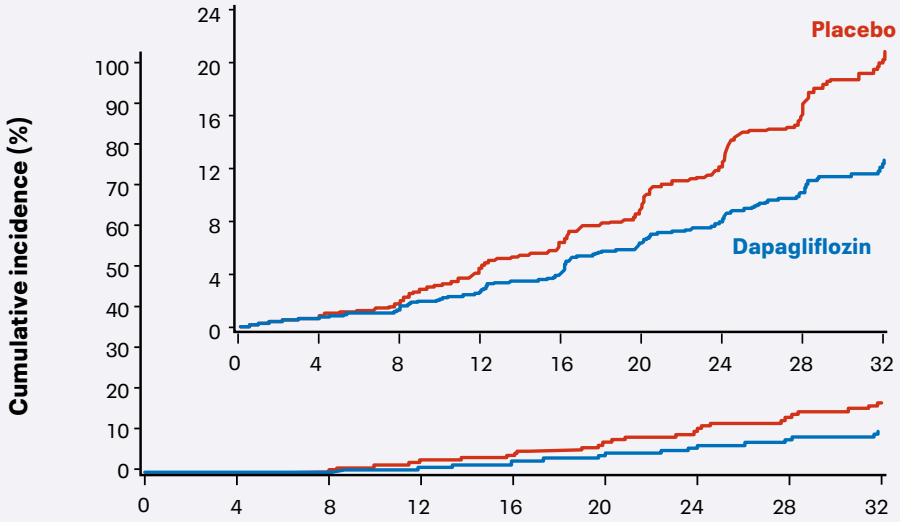
Regardless of T2D status among patients with chronic kidney disease, participants who took dapagliflozin had a lower risk of the primary composite outcome:

- Sustained decline in eGFR of at least 50%
- End-stage kidney disease
- Death from renal causes
- Death from cardiovascular causes

Dapagliflozin is the only SGLT2i proven to both reduce the risk of all-cause mortality and slow the decline in eGFR ≥50% in patients with CKD, with or without diabetes vs placebo on top of standard care

Primary Composite Outcome

HR 0.61 (95% CI, 0.51, 0.72)
p<0.001



No. at risk									
Placebo	2152	1993	1936	1858	1791	1664	1232	774	270
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309

Adapted from: Heerspink, H. J. L. *et al* (2020)[22]

DECLARE-TIMI Trial – T2D[21]

17,160
participants

who had or who were at risk for atherosclerotic cardiovascular disease (ASCVD) received either dapagliflozin 10mg once daily or placebo when added to background therapy or on top of standard of care

Study population was representative of the primary care population, with multiple risk factors for ASCVD such as dyslipidaemia, hypertension or use of tobacco[21]

Dapagliflozin reduced the rate of cardiovascular death or hospitalisation for heart failure (hHF)

DAPA-HF Trial – heart failure with reduced ejection fraction (HFrEF) ± T2D[26]

4,744
patients

with New York Heart Association class II, III, or IV heart failure and an ejection fraction of 40% or less received either dapagliflozin 10mg once daily or placebo, on top of standard care

The risk of worsening HF or death was lower among those receiving dapagliflozin REGARDLESS of T2D status

Reduced risk of CV death and all-cause mortality compared with placebo

DELIVER Trial – heart failure with preserved ejection fraction (HFpEF) ± T2D[27]

6,263
participants

who had or who were at risk for ASCVD and had an LVEF of >40% received either dapagliflozin 10mg once daily or placebo, on top of standard care

Dapagliflozin lowered the risk of worsening HF or cardiovascular death in patients with HF and mildly reduced or preserved ejection fraction

Take the possibility of side effects into account

Dapagliflozin has a consistent safety profile for patients with CKD.[6] Common adverse effects (reported in ≥2% of subjects, ≥1% more and ≥3 more subjects treated with dapagliflozin 10mg compared to placebo), included **urinary tract and genital infections, rash, back pain, dizziness, and dysuria/polyuria**.[6]

Rare, and very rare adverse reactions include diabetic ketoacidosis (when used in patients with T2D), Fournier's gangrene, angioedema and tubulointerstitial nephritis.[6] Patients should be informed of the possible risks when taking dapagliflozin, and ways that they can reduce the possibility of these occurring. Refer to the SmPC for full details of adverse events.[6]

Case study highlight: Debbie's GP has discussed the possible side effects of an SGLT2i, and given her advice on steps she can take to reduce the likelihood of them occurring:

- As there is an increased risk of genital infections, genital washing instructions are given[18]
- Sick day guidance: if unwell, temporarily stop metformin, lisinopril and SGLT2i[18]
- Routine preventative diabetic foot care[1]

Contraindications

Those who are hypersensitive to dapagliflozin or its excipients should not take dapagliflozin.[6] The SmPC should be consulted before initiating treatment.[6]

For more information about the safety of dapagliflozin, scan here.

What's next for Debbie?

Debbie is pleased to have started treatment with dapagliflozin and finds the once daily dosing schedule easy to stick to along with her other medications. She is looking forward to spending more time with her family and being able to help look after her grandchildren for longer.

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Prescribing information

FORXIGA® (dapagliflozin) 5MG & 10MG FILM-COATED TABLETS.

Consult Summary of Product Characteristics before prescribing.

Indications: Adults: Type 2 Diabetes Mellitus: For the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise, as monotherapy when metformin is considered inappropriate due to intolerance, or in addition to other medicinal products for the treatment of type 2 diabetes. **Heart Failure:** For the treatment of symptomatic chronic heart failure. **Chronic Kidney Disease:** for the treatment of chronic kidney disease. **Children aged 10 years and above: Type 2 Diabetes Mellitus:** For the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise, as monotherapy when metformin is considered inappropriate due to intolerance, or in addition to other medicinal products for the treatment of type 2 diabetes.

Presentation: Film-coated tablets. 5mg or 10mg of dapagliflozin (as propanediol monohydrate). Each 5mg tablet contains 25mg of lactose. Each 10mg tablet contains 50mg of lactose.

Dosage and Administration: Forxiga can be taken at any time of day with or without food. Tablets should be swallowed whole. **Adults: Type II Diabetes Mellitus:** The recommended dose is 10mg once daily. Consider a lower dose of insulin or insulin secretagogue such as a sulphonylurea when used in combination with dapagliflozin to reduce the risk of hypoglycaemia. **Heart Failure:** The recommended dose is 10mg once daily. **Chronic kidney disease:** The recommended dose is 10mg dapagliflozin once daily. **Renal impairment:** No dose adjustment is required. **Mild or moderate hepatic impairment:** No dose adjustment is required. **Severe hepatic impairment:** Starting dose of 5mg is recommended, if well tolerated, dose may be increased to 10mg. **Elderly:** ≥65 years: No dose adjustment is required. **Children and adolescents: Type II Diabetes Mellitus ≥10 years:** No dose adjustment required. The recommended dose is 10mg once daily. Consider a lower dose of insulin or insulin secretagogue such as a sulphonylurea when used in combination with dapagliflozin to reduce the risk of hypoglycaemia. **Children <10 years:** Safety and efficacy not yet established. **Heart Failure / Chronic kidney disease: Children <18 years:** Safety and efficacy not yet established.

Contraindications: Hypersensitivity to dapagliflozin, or excipients.

Warnings and Precautions: Renal impairment: There is limited experience with initiating treatment with dapagliflozin in patients with eGFR < 25 mL/min/1.73m^2, and no experience with initiating treatment in patients with eGFR < 15 mL/min/1.73m^2. Therefore, it is not recommended to initiate treatment with dapagliflozin in patients with eGFR < 15 mL/min/1.73m^2. The glucose lowering efficacy of dapagliflozin is dependent on renal function and is reduced in patients with eGFR < 45 mL/min/1.73m^2 and is likely absent in patients with severe renal impairment. In patients with moderate renal impairment (eGFR < 60 mL/min/1.73m^2), a higher proportion of patients treated with dapagliflozin had adverse reactions of increase in parathyroid hormone (PTH) and hypotension, compared with placebo. **Hepatic impairment:** Exposure is increased in patients with severe hepatic impairment. **Use in patients at risk of volume depletion and/or hypotension:** Dapagliflozin increases diuresis which may lead to a modest decrease in blood pressure, it may be more pronounced in patients with very high blood glucose concentrations. Exercise caution in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients on anti-hypertensive therapy with a history of hypotension or elderly patients. Careful monitoring of volume status and electrolytes is recommended in conditions leading to volume depletion, such as acute gastrointestinal illness. In volume depleted patients temporary interruption of dapagliflozin is recommended until volume depletion is corrected. **Diabetic ketoacidosis (DKA):** SGLT2 inhibitors should be used with caution in patients with increased risk of DKA. Patients who may be at higher risk of DKA include patients with a low beta-cell function reserve (e.g. type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse. The risk of DKA must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level. Before initiating dapagliflozin, factors in patient history that may predispose to ketoacidosis should be considered. Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patient's. Measurement of blood ketone level is preferred to urine. Treatment with dapagliflozin may be restarted when the ketone values are normal and the patient's condition has stabilised. Rare cases of DKA, including life-threatening and fatal cases, have been reported in patients treated with SGLT2 inhibitors, including dapagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14mmol/L (250mg/dL). In patients where DKA is suspected or diagnosed, dapagliflozin treatment should be stopped immediately. Restarting SGLT2 inhibitor treatment in patients with previous DKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved. Dapagliflozin should not be used for treatment of patients with type 1 diabetes. **Necrotising fasciitis of the perineum (Fournier's gangrene):** Post-marketing cases have been reported in female and male patients taking SGLT2 inhibitors. Urgent surgical intervention and antibiotic treatment required. Advise patients to seek medical attention if they experience a combination of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Either uro-genital infection or perineal abscess may precede necrotising fasciitis. If suspected discontinue Forxiga and institute prompt treatment (including antibiotics and surgical debridement). **Urinary tract infections:** Temporary interruption of dapagliflozin should be considered when treating pyelonephritis or urosepsis. **Elderly (≥65 years):** Elderly patients are more likely to have impaired renal function, be treated with medicines such as anti-hypertensives or diuretics, and be at a

greater risk of volume depletion. **Cardiac failure:** Experience with dapagliflozin in NYHA class IV is limited. **Chronic kidney disease:** There is no experience with dapagliflozin for the treatment of chronic kidney disease in patients without diabetes who do not have albuminuria. Dapagliflozin has not been studied for the treatment of chronic kidney disease in patients with polycystic kidney disease, glomerulonephritis with flares (lupus nephritis or ANCA-associated vasculitis), ongoing or recent requirements of cytotoxic, immunosuppressive or other immunomodulating renal therapy, or in patients who received an organ transplant. **Increased haematocrit:** Increased haematocrit has been observed with dapagliflozin treatment. Patients with pronounced elevations in haematocrit should be monitored and investigated for underlying haematological disease. **Lower limb amputations:** Counsel patients with diabetes on routine preventative foot care. An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term, clinical studies with SGLT2 inhibitors. **Urine laboratory assessments:** Patients will test positive for glucose in the urine due to mechanism of action. **Lactose:** Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take Forxiga.

Drug Interactions: Diuretics: Dapagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension. **Insulin and insulin secretagogues:** Consider a lower dose of insulin or insulin secretagogue in combination with dapagliflozin to reduce the risk of hypoglycaemia. **Effect of dapagliflozin on other medicinal products:** Dapagliflozin may increase renal lithium excretion and the blood lithium levels may be decreased. **Interference with 1,5-AG assay:** Monitoring glycaemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors. Alternative methods should be used.

Pregnancy and Lactation: Not recommended during the second and third trimesters of pregnancy. Treatment should be discontinued when pregnancy is detected. Do not use whilst breast-feeding.

Ability to Drive and Use Machines: Alert patients on the risk of hypoglycaemia when dapagliflozin is used in combination with a sulphonylurea or insulin.

Undesirable Events: Consult SmPC for full list of side effects. **Very common** (≥1/10): Hypoglycaemia (when used with SU or insulin). **Common** (≥1/100 to <1/10): Vulvovaginitis, balanitis and related genital infections, urinary tract infection, dizziness, rash, back pain, dysuria, polyuria, haematocrit increased, creatinine renal clearance decreased during initial treatment, dyslipidaemia. **Uncommon** (≥1/1,000 to < 1/100): Volume depletion. **Rare** (≥ 1/10,000 to < 1/1,000): Diabetic ketoacidosis. **Very Rare** (< 1/10,000): Angioedema, necrotising fasciitis of the perineum (Fournier's gangrene), tubulointerstitial nephritis.

Legal Category: POM.

Marketing Authorisation Number: PLGB 17901/0326, PLGB 17901/0325.

Presentation & Basic NHS Cost: Forxiga 5mg film-coated tablets 28: £36.59; Forxiga 10mg film-coated tablets 28: £36.59.

Business Responsible for Sale and Supply / Further information: AstraZeneca UK Ltd., 2 Pancras Square, London, N1C 4AG, UK.

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to AstraZeneca by visiting https://contactazmedical.astrazeneca.com or by calling 0800 783 0033.

Scan the QR code to access the FORXIGA® (dapagliflozin) prescribing information

AstraZeneca

A **once-daily dose of 10mg** makes prescribing and adherence to treatment **practical** and **simple**[6]

No dose adjustment is needed to begin treatment with dapagliflozin. However, patients with severe hepatic impairment should begin with a dose of 5mg once daily, which can be increased to 10mg if tolerated well[6]

Dapagliflozin **reduces all-cause mortality from renal causes** in patients **with CKD, with and without T2D** compared with placebo alongside standard care[20,21,25,26]

Dapagliflozin **reduced worsening renal decline** compared with placebo on top of standard of care[20,21,25,26]

Dapagliflozin has a **consistent safety profile in patients** with type 2 diabetes (based on the DECLARE-TIMI study)[20], and with CKD (based on the DAPA-CKD study)[21] alongside standard care

NICE guidance recommends a SGLT2i for treating patients with **T2D* and CKD**

*For patients with insufficiently controlled T2D, an SGLT2i can be used in addition to metformin, or as a monotherapy where metformin is inappropriate.[1]

Scan here for more information about prescribing and dosing for dapagliflozin

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to AstraZeneca by visiting https://contactazmedical.astrazeneca.com or by calling 0800 783 0033.

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