Cardiovascular protection* across cardiovascular, renal and metabolic conditions using Empagliflozin

*By reducing risk for people with CKD, HF or T2D

KHADIJA HAFIDH MD DUBAI ACADEMIC HEALTH CORPORATION





Disclosure

I am contracted by Boehringer Ingelheim to conduct this session.

I have no financial interest in **Boehringer Ingelheim**

The views expressed in this presentation are my own and do not reflect the official position or policy of the Dubai Academic Health Corporation.



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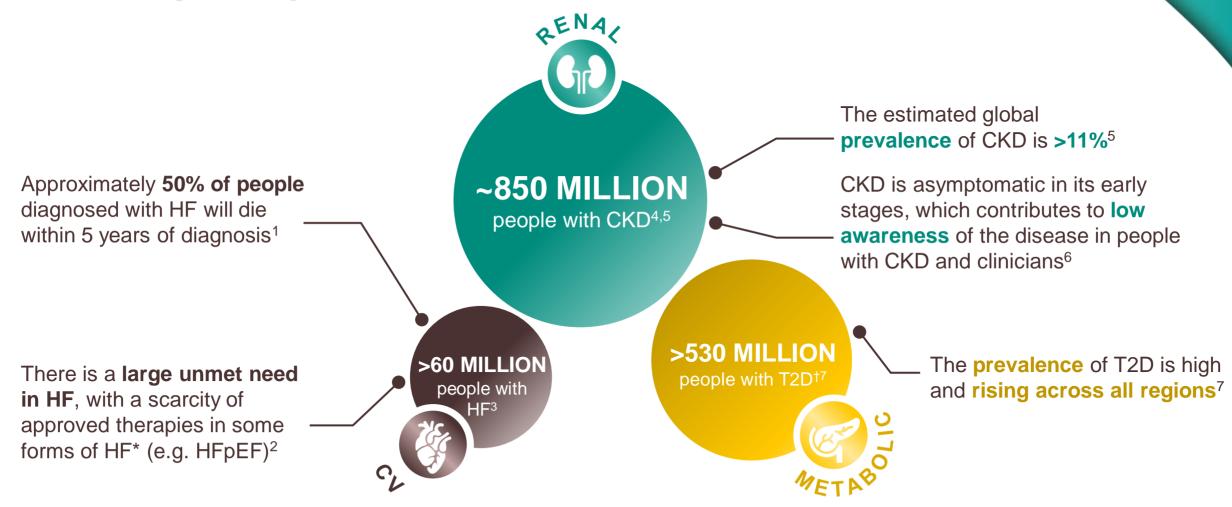
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CV, renal and metabolic conditions pose a high disease burden globally



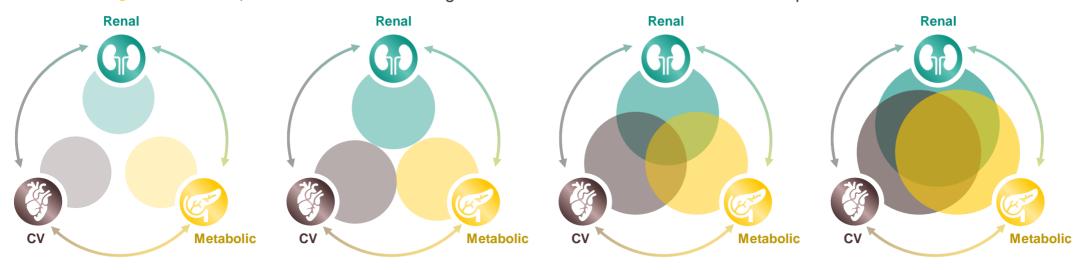


Early and multifactorial intervention is the best way to help protect by reducing the amplifying risks associated with interrelated CV, renal and metabolic conditions

Early screening, diagnosis and intervention can delay the consequences of CV, renal or metabolic conditions including CV death¹⁻³



Guideline recommendations endorse a **multifactorial approach** in people with CKD, HF and/or T2D to manage risk factors and reduce their risk of complications ^{1–3}

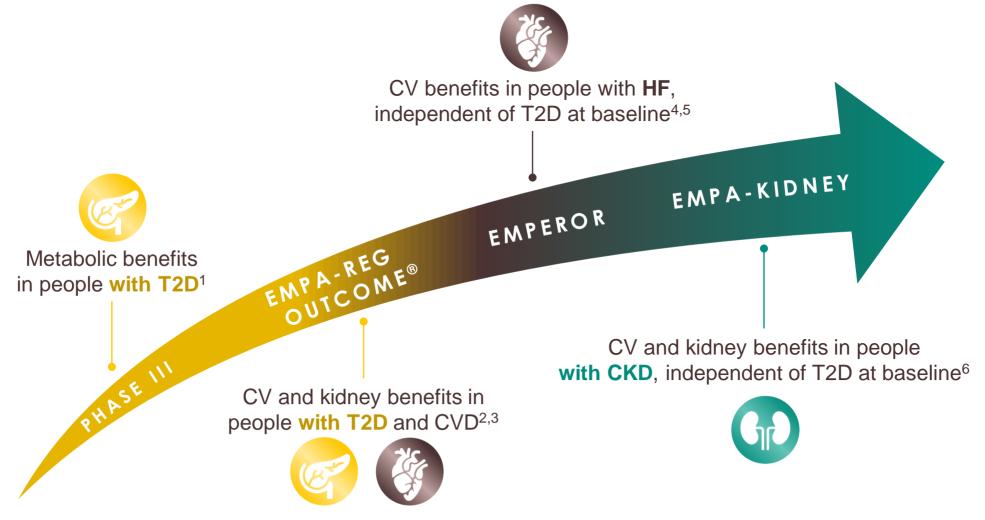


Patient diagnosed with a CV, renal or metabolic condition (CKD, HF or T2D) Patients may develop additional CV, renal or metabolic risk factors Patients can progress to two or more CV, renal or metabolic conditions Coexistence of two or all three CV, renal or metabolic conditions together is associated with increased mortality^{4–7}

Time

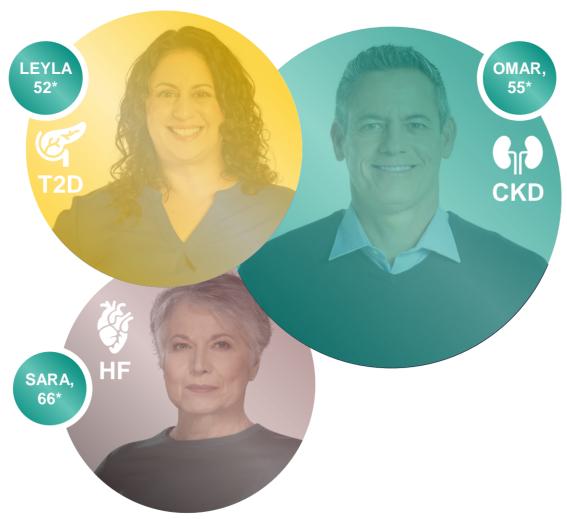


Empagliflozin has demonstrated improved glucose control in people with T2D, as well as CV and kidney benefits in people with CKD and/or HF, independent of T2D





Empagliflozin provides proven CV, renal and metabolic benefits in people who have CKD, HF or T2D





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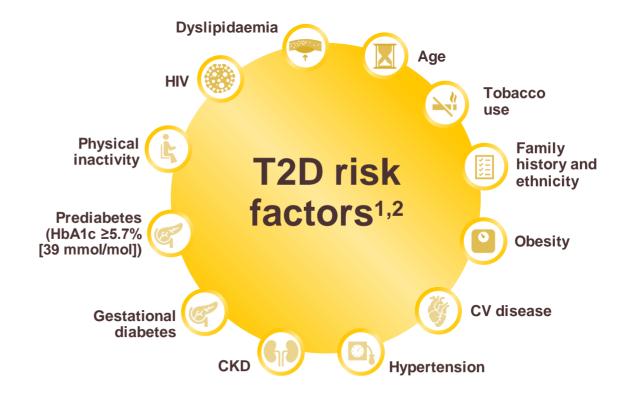
LEYLA* has T2D and is at increased risk of CV, renal and metabolic complications





- Diagnosed with T2D in the last 3 months
- · Has hypertension and dyslipidaemia
- Improving diet and exercise; not on glucose-lowering medication
- BMI: 29 kg/m²
- HbA1c: 7.8% (61.7 mmol/mol)







Early diagnosis and intervention in T2D is crucial for patients with known risk factors¹







Diagnosis of T2D¹



Determine simple risk factors (e.g. older age, high BP, obesity, family history)



Measure blood glucose levels (HbA1c, FPG or 2-hr PG)†





Monitor CV risk factors and kidnev function regularly

People with T2D are at **very high CV risk** if they have any of the following²:



- History of CV disease CV disease risk factors



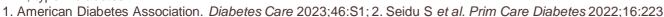
Diagnosis of early onset T2D (aged <40 years)



- eGFR <60 ml/min/1.73 m² Albuminuria

All other people with T2D are considered to be at high CV risk

BP, blood pressure; CV, cardiovascular; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; PG, plasma glucose; T2D, type 2 diabetes



^{*}Not an actual patient

[†]Choice and availability of diagnostic tests may vary across countries/regions; in the absence of unequivocal hyperglycaemia, confirm diagnosis of T2D with two abnormal screening test results1

How would you reduce the risk of CV, renal and metabolic complications to help protect patients like Leyla*?



Reducing the risk of CV and kidney complications should be a patient's top priority, so discussing the importance of an early, multifactorial approach for improving long-term outcomes is key^{1,2}

Shared decision-making involves an open discussion with the patient, integrating medical considerations and the patient's preferences, and can improve treatment adherence^{3–5}

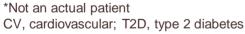


"

How will treatment impact my day-to-day life? It is important that it does not affect my time with my kids"



I worry about ending up with major complications if we don't manage my T2D"



 $[\]mathbf{E}^3$

Empagliflozin provides multiple metabolic benefits to patients early in their T2D journey



Empagliflozin 25 mg + metformin*

HbA1c

Baseline 7.9%

Reduction of 0.8% at Week 24^{†1,2}

Baseline ≥8.5%
Reduction of 1.5%
at Week 24^{‡3}

Systolic BP

Baseline 130 mmHg

Reduction of 5.2 mmHg at Week 24§1,2

Weight

Baseline BMI 29.7

Reduction of 2.5 kg at Week 24^{II1,2}

Baseline BMI ≥35

Reduction of 3.4 kg at Week 24 and 4.8 kg at Week 76^{¶3}

prescribing Empagliflozin early help a patient with elevated CV risk like Leyla^{††}



Reductions in body weight and systolic blood pressure were not primary endpoints² ^{††}Not an actual patient

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Summary and conclusion



Sara* has been diagnosed with HF and is at increased risk of CV, renal and metabolic complications





- LVEF of 55–60%
- On ACEi and β-blocker
- Has atrial fibrillation
- Worsening dyspnoea on exertion



Presence of signs and symptoms of HF should prompt referral to cardiologist¹

Universal definition of HF¹

Symptoms and/or signs of HF caused by a structural and/or functional cardiac abnormality

And corroborated by at least one of the following

Elevated natriuretic peptide levels†

or

Objective evidence of cardiogenic, pulmonary or systemic congestion

Common symptoms and signs that patients may present with include¹:

- Breathlessness
- Orthopnoea or 'bendopnoea' (dyspnoea on bending over)
- · Paroxysmal nocturnal dyspnoea
- · Reduced exercise tolerance/inability to exercise
- · Fatigue, tiredness
- Peripheral oedema (ankle, sacral, scrotal)
- Swelling of parts of the body other than ankles

Evidence from diagnostic tests include^{1,2}:

- · Abnormal findings on electrocardiogram
- NT-proBNP ≥125 pg/ml or BNP ≥35 pg/ml
- Chest X-ray

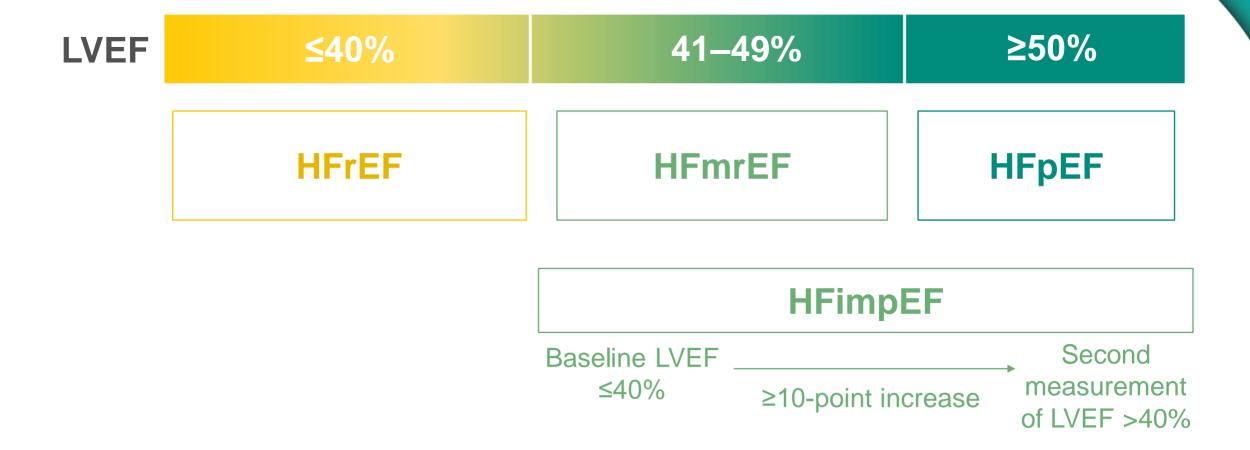


Specialist cardiology service



Guideline-directed medical therapy differs across classifications of HF based on LVEF







How would you reduce the risk of CV, renal and metabolic complications to help protect patients like Sara*?



Reducing the risk of CV, renal and metabolic complications should be a patient's top priority, so discussing the importance of an early, multifactorial approach for improving long-term outcomes is key¹

After diagnosis, the management of HF is often shared between PCP and cardiologist.

Shared decision-making involves an open discussion with the patient, integrating medical considerations and the individual's preferences, and can improve treatment adherence.^{2–5}

*Not an actual patient; †Except in cases where there is rationale for discontinuation



My ankles are swollen and I don't understand why. Is this connected to my other symptoms or medication?"



When will my quality of life get better again?"



I can't even walk down the street without getting out of breath"

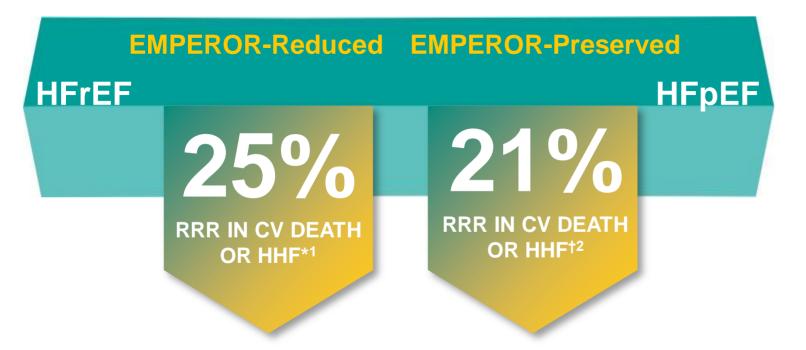
Continue guideline-directed medical therapy, such as Empagliflozin in a person with HF (irrespective of T2D)†





Empagliflozin provides protection for people with HF across the LVEF spectrum by reducing the risk of CV death or HHF







Consistent efficacy across subgroups including^{1–3}:

- With or without T2D
- With or without CKD

HR 0.75; 95% CI 0.65, 0.86; p<0.001 ARR=5.3%: NNT=19

HR 0.79: 95% CI 0.69, 0.90: p<0.001 ARR=3.3%: NNT=31



ARR, absolute risk reduction; CKD, chronic kidney disease; CV, cardiovascular; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HHF, hospitalisation for heart failure; LVEF, left ventricular ejection fraction; NNT, number needed to treat; RRR, relative risk reduction; T2D, type 2 diabetes See notes for footnotes

In the approved patient populations

Guidelines recommend the use of SGLT2 inhibitors, such as Empagliflozin, across the CV, renal and metabolic spectrum



Guidelines recommend SGLT2 inhibitors for people with HF¹⁻³

HFrEF

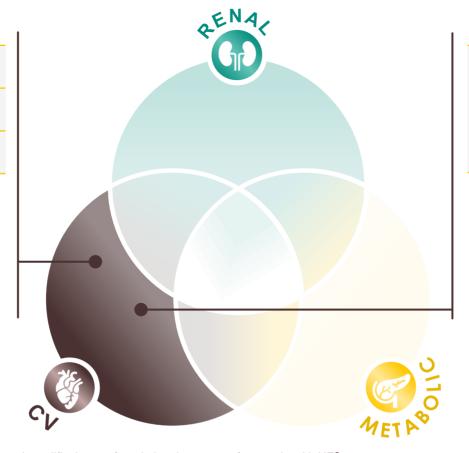
2021 ESC Guidelines¹

2021 CCS/CHFS Guidelines²

2022 AHA/ACC/HFSA Guidelines³

ESC recommend SGLT2 inhibitors as first-line HFrEF therapy*1

SGLT2 inhibitors are recommended as foundational therapy for patients with HF1-3



HFpEF

2022 AHA/ACC/HFSA Guidelines³

SGLT2 inhibitors have the **strongest**recommendation (class IIa) within available
therapies for both HFmrEF (LVEF 41–49%)
and HFpEF (LVEF ≥50%)



*This recommendation is only for the use of empagliflozin or dapagliflozin as a foundational treatment for people with HF²
ACC, American College of Cardiology; AHA, American Heart Association; CCS, Canadian Cardiovascular Society; CHFS, Canadian Heart Failure Society; CV, cardiovascular; ESC, European Society of Cardiology; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFSA, Heart Failure Society of America; LVEF, left ventricular ejection fraction; SGLT2, sodium-glucose co-transporter-2

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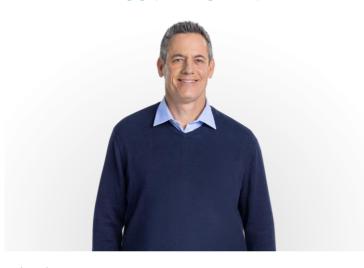


Omar* has been diagnosed with CKD and is at increased risk of CV, renal and metabolic complications





- Has hypertension and dyslipidaemia
- · Family history of CV disease
- On ACEi and statin
- BMI: 29.3 kg/m²
- eGFR: 68 ml/min/1.73 m²
- UACR: 40 mg/g (4.52 mg/mmol)





*Not an actual patient

ACEi, angiotensin-converting enzyme inhibitor; BMI, body mass index; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio



Early diagnosis and intervention in CKD is crucial for patients with known risk factors¹











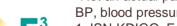
Determine known risk factors (e.g. high BP, T2D, CV disease, obesity) and/or signs and symptoms of CKD







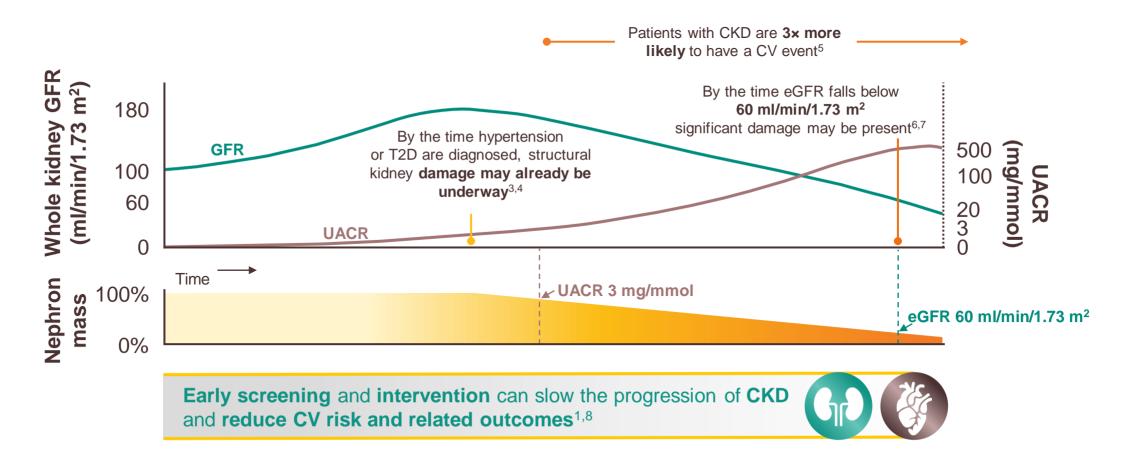
These tests provide the evidence needed for an early diagnosis²



CKD is a progressive disease and acts as a CV risk multiplier^{1,2}



By the time treatment for CKD is initiated, it is often too late





How would you reduce the risk of CV, renal and metabolic complications to help protect patients like Omar*?



Reducing the risk of CV, renal and metabolic complications should be a patient's top priority, so discussing the importance of an early, multifactorial approach for improving long-term outcomes is key¹

Shared decision-making involves an open discussion with the patient, integrating medical considerations and the patient's preferences, and can improve treatment adherence^{2–4}





How will treatment impact my day-to-day life? It is important that it does not affect my travelling for work"



I work long hours, so I need a medication that is easy to take"



I would hate to end up needing dialysis"



People with CKD can be managed in primary care; however, specialist referral may be required for those at greater risk of progression or complications



Factors that should prompt referral to specialist kidney care services include:









Specialist kidney

care services



- AKI or abrupt sustained fall in eGFR¹
- Progression of CKD defined as: decline in eGFR category with ≥25% drop in eGFR from baseline and/or rapid progression of CKD (sustained eGFR decline ≥5 ml/min/1.73 m² per year)¹
- Moderately increased risk of CKD progression*^{1–3}



Hereditary kidney disease¹



• Recurrent or extensive nephrolithiasis (kidney stones)1



CKD and hypertension refractory to treatment with ≥4 antihypertensive agents¹



Signs of nephrotic syndrome (heavy proteinuria with low serum albumin) or unexplained haematuriat



- Persistent abnormalities of serum potassium, calcium or phosphate^{1,4}
- Anaemia of unknown cause⁴

See slide notes for abbreviations

*Moderately increased risk of CKD progression¹¬³: eGFR <30 ml/min/1.73 m² or significant albuminuria (UACR ≥300 mg/g (≥30 mg/mmol) or AER ≥300 mg/24 hours, approximately equivalent to PCR ≥500 mg/g (≥50 mg/mmol) or PER ≥500 mg/24 hours) or high risk of progression to ESKD according to KFRE (e.g. >3% to >5% risk at 5 years)

1. Inker LA *et al. Am J Kidney Dis* 2014;63:713; 2. Bhachu HK *et al. Kidney Int Rep* 2021;6:2189; 3. National Institute for Health and Care Excellence. Chronic kidney disease: assessment and management. 2021. https://www.nice.org.uk/guidance/ng203 (accessed Mar 2023); 4. UK Kidney Association. The UK eCKD Guide. 2017. https://ukkidney.org/health-professionals/information-resources/uk-eckd-guide/referral (accessed Mar 2023)



In EMPA-KIDNEY, Empagliflozin reduced kidney disease progression or risk of CV death, and reduced all-cause hospitalisation, in a broad population of people who have CKD with or without T2D*^{†1,2}



28%

RRR IN

KIDNEY DISEASE

PROGRESSION

OR CV DEATH

HR 0.72 95% CI 0.64, 0.82 p<0.001

reduction; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio

14%

RRR IN FIRST &
RECURRENT
ALL-CAUSE

HR 0.86 95% CI 0.78, 0.95 p=0.003

HOSPITALISATION[‡]



Consistent benefits proven across the patients you see in your practice, including²:

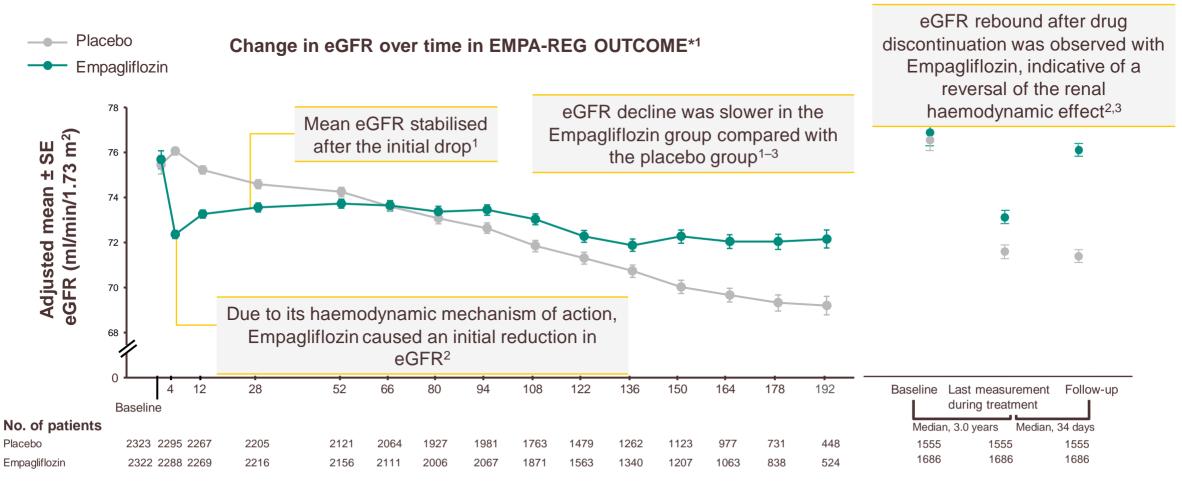
- With and without T2D
- Mildly to severely reduced eGFR (<90 to ≥20 ml/min/1.73 m²)
- With and without prior CVD
- With or without background use of RAASi§

*Adult patients with an eGFR ≥20 to <45 ml/min/1.73 m², or an eGFR ≥45 to <90 ml/min/1.73 m² with a UACR ≥200 mg/g²; †In the EMPA-KIDNEY trial, a randomised, parallel-group, double-blind, placebo-controlled study of 6609 patients with CKD, the efficacy and safety of Empagliflozin 10 mg (n=3304) were evaluated vs placebo (n=3305). The primary endpoint in the EMPA-KIDNEY trial was a composite of CV death or progression of kidney disease. Patients treated with Empagliflozin experienced a 28% RRR in this endpoint (HR 0.72; 95% CI 0.64, 0.82; p<0.001)²; ‡Hospitalisation for any cause was a key secondary outcome of the EMPA-KIDNEY trial. The analysis of hospitalisations for any cause included the first and all subsequent events (Empagliflozin, 1611 hospitalisations in 960 patients; placebo, 1895 hospitalisations in 1035 patients)²; §At baseline, 85.7% of patients on Empagliflozin and 84.6% of patients on placebo were taking a RAASi² CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; RAASi, renin–angiotensin–aldosterone system inhibitor; RRR, relative risk



In people with T2D at high risk for CV events, the rate of kidney function decline after the initial decrease was consistently slower with Empagliflozin than with placebo





See slide notes for abbreviations



^{*}The baseline to Week 192 graph is based on an MMRM analysis in patients treated with ≥1 dose of study drug who had a baseline and post-baseline measurement. The baseline to follow-up graph is based on a prespecified analysis of a covariance model in patients who underwent measurements at all three time points

In the approved patient populations

Guidelines recommend the use of SGLT2 inhibitors, such as Empagliflozin, across the CV, renal and metabolic spectrum

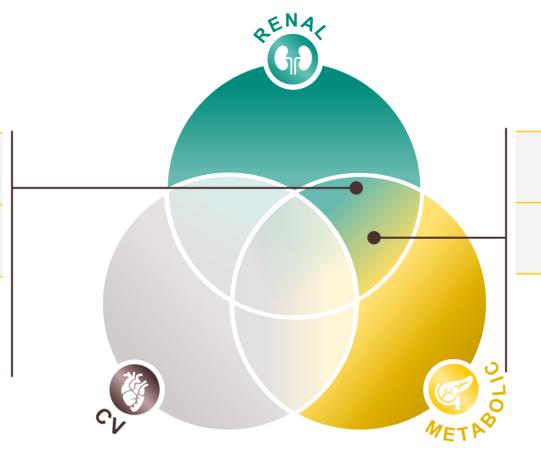


Guidelines recommend SGLT2 inhibitors for people with T2D and CKD^{1–3}

KDIGO 2022¹

ADA-KDIGO 2022²

SGLT2 inhibitors are recommended as first-line therapy for people with T2D and CKD



ADA 20233

ADA-EASD 20224

SGLT2 inhibitors are recommended as first-line therapy for people with T2D and CKD



ADA, American Diabetes Association; CKD, chronic kidney disease; CV, cardiovascular; EASD, European Association for the Study of Diabetes; KDIGO, Kidney Disease: Improving Global Outcomes; SGLT2, sodium-glucose co-transporter-2; T2D, type 2 diabetes

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Int* 2022;102:S1; 2. de Boer IH *et al. Diabetes Care*. 2022;45:3075; 3. American Diabetes Association. *Diabetes Care* 2023;45:S1; 4. Davies MJ *et al. Diabetes Care* 2022;45:2753

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Summary and conclusion



Empagliflozin is easy to use across a broad range of people with CKD, HF or T2D





- In CKD and HF, Empagliflozin can be initiated down to an eGFR of 20 ml/min/1.73 m²
- For people with T2D and CV disease, Empagliflozin can be initiated down to 30 ml/min/1.73 m^{2‡}

No titration required for most patients[†]

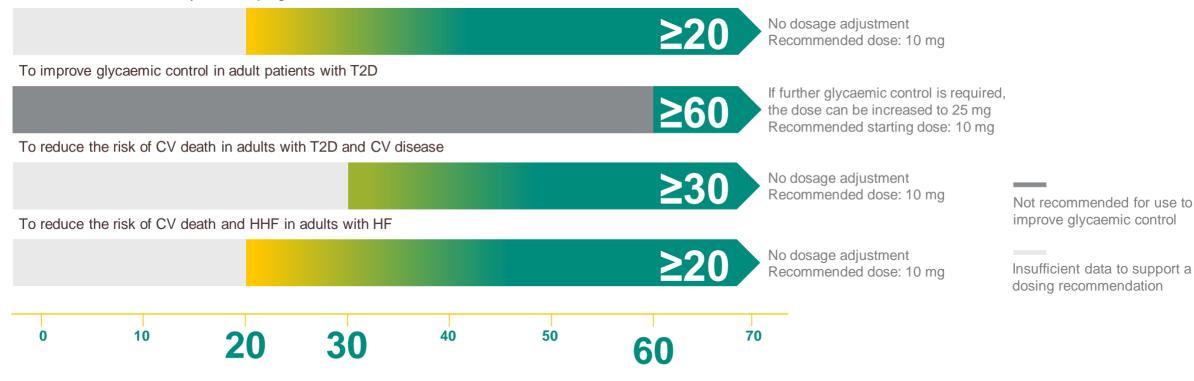


^{*}Tablets can be taken with or without food, swallowed whole with water; †Increase to 25 mg once daily in people with T2D who tolerate 10 mg and need additional glycaemic control; ‡For people with T2D without CV disease, Empagliflozin can be initiated down to 45 ml/min/1.73 m²

Empagliflozin can be initiated with an eGFR as low as 20 ml/min/1.73 m² in people with HF or CKD*

Empagliflozin initiation dosing recommendations based on indication and kidney function[†]

To reduce the risk of kidney disease progression or CV death in adults with CKD with or without T2D



eGFR (ml/min/1.73 m²)

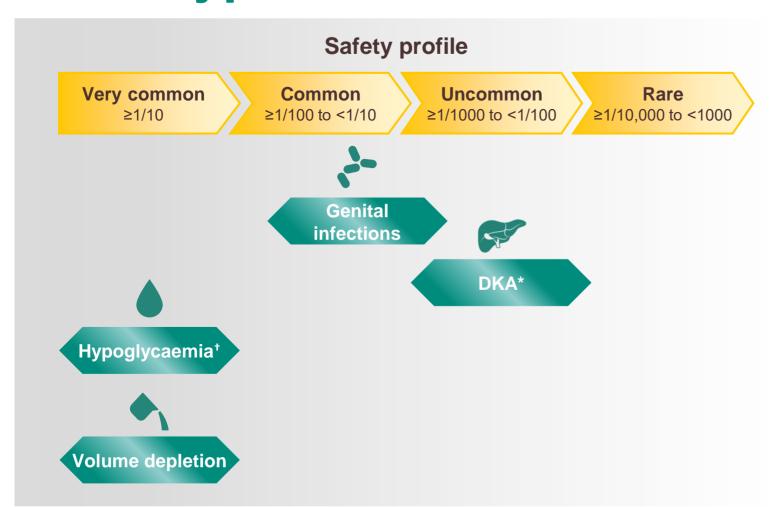
CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hospitalisation for heart failure; T2D, type 2 diabetes Empagliflozin (empagliflozin) summary of product characteristics. Sep 2022



^{*}Please see the summary of product characteristics for dosing details

[†]Because the glycaemic lowering efficacy of Empagliflozin is reduced in patients with moderate renal impairment and likely absent in patients with severe renal impairment, if further glycaemic control is needed, the addition of other anti-hyperglycaemic agents should be considered

Empagliflozin has an established safety and tolerability profile



Contraindications and precautions

- Empagliflozin should not be used for the treatment of patients with:
 - Type 1 diabetes
 - Severe hepatic impairment or patients on dialysis
 - Hypersensitivity to the active substance or to any of the excipients
- In patients aged 75 years and older, an increased risk of volume depletion should be taken into account



Empagliflozin has a placebo-like incidence of hypoglycaemia when added to metformin



Rare cases of Fournier's gangrene have been reported in people with T2D treated with SGLT2 inhibitors



Empagliflozin[®] provides triple protection by reducing risk for a broad range of your patients with¹:



HF

CKD

38%

RRR IN CV DFATH*1,2

HR 0.62; 95% CI 0.49, 0.77; p<0.001 ARR 2.2% NNT 46

32%

ALL CAUSE MORTALITY *1,2

HR=0.68; 95% CI: 0.57, 0.82;

25%

RRR IN
CV DEATH OR HHF
IN LVEF ≤40%^{†1,3}

HFrFF

HR 0.75; 95% CI 0.65, 0.86; p<0.001 ARR 5.3% NNT 19

21%

HFpEF

RRR IN CV DEATH OR HHF IN LVEF >40%^{‡1,4}

HR 0.79; 95% CI 0.69, 0.90; p<0.001 ARR 3.3% NNT 30

28%

RRR IN KIDNEY DISEASE PROGRESSION OR CV DEATH§5

HR 0.72; 95% CI 0.64, 0.82; p<0.001 ARR 3.8% NNT 26

In addition, Empagliflozin provides metabolic benefits in T2D, including reductions in HbA1c, systolic blood pressure and weight 1,6

Early intervention with Empagliflozin can help protect* our patients at CV risk



*Early screening, diagnosis and intervention with SGLT2 inhibitors, such as Empagliflozin, can protect people with:

CKD – by reducing risk of CV death or kidney disease progression¹

HF (both HFrEF and HFpEF) – by reducing risk of CV death or hospitalisation for HF^{2,3}

T2D and CV disease – by reducing risk of CV death⁴



Holistic management is required for people with CKD, HF or T2D due to the interrelated CV, renal and metabolic systems^{5,6}



Established safety profile, well tolerated and convenient once-daily oral dosing⁷

International CKD, HF and T2D guidelines recommend the use of an SGLT2 inhibitor like **Empagliflozin as early foundational therapy**^{8–10}





THANK YOU

