Kidney benefits and safety of SGLT2 inhibitors clarified

Two large meta-analyses, published in *JAMA*, show that the benefits of SGLT2 inhibitors on chronic kidney disease (CKD) progression and hospitalisation for heart failure are similar regardless of diabetes status, uACR or eGFR levels, as is the low risk of adverse effects. Since absolute benefits vary depending on the risk of CKD progression, diabetes status and whether heart failure is present, the authors caution that until prices reduce, cost-effectiveness should continue to be considered. A separate meta-analysis of four large randomised controlled trials of empagliflozin, published in *The Lancet Diabetes & Endocrinology*, demonstrated reduced risk of acute kidney injury and chronic kidney outcomes irrespective of the initial eGFR dip, diabetes status, baseline eGFR or albuminuria level. The degree of absolute benefit with SGLT2 inhibitors compared to placebo across all three meta-analyses greatly exceeded the risk of safety events such as diabetic ketoacidosis, amputation and the small increased risk of fracture in those with type 2 diabetes. Accompanying commentaries highlight that for greatest benefit, these drugs should be initiated early and that, at present, they remain underprescribed even in those most likely to benefit.

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Sodium–glucose cotransporter 2 (SGLT2) inhibitors have been demonstrated to reduce the risk of kidney disease progression, kidney failure and acute kidney injury in many groups with chronic kidney disease (CKD), as well as reducing risk of cardiovascular death, hospitalisation for heart failure and hospitalisation for other conditions; however, they remain underprescribed in groups who would benefit from them. Although current guidelines recommend use of SGLT2 inhibitors in people with type 2 diabetes and/or CKD, uncertainties remain about whether all groups benefit, including those with lower risk of CKD progression and those at risk of large eGFR dips following initiation, in whom there are concerns regarding acute kidney injury (Zoccali and Mallamaci, 2025).

The present studies

Three recent meta-analyses sought to expand the evidence base and clarify whether SGLT2 inhibitor benefits occur over the full ranges of eGFR and uACR, the impact of diabetes status on renal benefits and, in the third meta-analysis looking solely at empagliflozin treatment, whether benefits occur in those with slowly progressive CKD (e.g. low albuminuria) or those at risk of larger acute eGFR declines when initiating empagliflozin.

Meta-analysis 1: SGLT2 inhibitors and kidney outcomes by eGFR and uACR

In their meta-analysis of individual patient data from ten randomised, double-blind, placebo-controlled trials of SGLT2 inhibitors licensed to reduce CKD progression participating in the SGLT2 inhibitor Meta-Analysis Cardio-Renal Triallists Consortium (SMART-C), Neuen and colleagues aimed to identify whether the level of eGFR or uACR modifies the effects of the drugs on kidney outcomes.

Among the more than 70 000 participants, CKD progression occurred in 3.3%. Overall, SGLT2 inhibitor treatment reduced this risk compared with placebo, and there was no significant difference in benefit between subgroups with eGFRs ranging from ≥60 to <30 mL/min/1.73 m^2, or with albuminuria levels ranging from ≤3 mg/mmol to >30 mg/mmol. The benefits were also consistent in people with stage 4 CKD and those with minimal albuminuria.

Kidney failure occurred in 1.4% of participants; both acute kidney injury and kidney failure were reduced with SGLT2 inhibitors

Citation: Brown P (2025) Diabetes Distilled: Kidney benefits and safety of SGLT2 inhibitors clarified. *Diabetes & Primary Care* **27**: 197–99

Table 1. Outcome rates in SGLT2 inhibitor versus placebo recipients, with or without type 2 diabetes.

Outcome	Event rates (per 1000 person-years) in SGLT2i vs placebo recipients	
	Type 2 diabetes	No diabetes
Kidney disease progression	33 vs 48 (HR 0.65)	32 vs 46 (HR 0.74)
Acute kidney injury	14 vs 18 (HR 0.77)	13 vs 18 (HR 0.72)
Hospitalisation (any cause)	202 vs 231 (HR 0.90)	203 vs 237 (HR 0.89)
Death (any cause)	42 vs 47 (HR 0.86)	42 vs 48 (HR 0.91)

versus placebo across the spectrum of eGFR and albuminuria levels.

Meta-analysis 2: SGLT2 inhibitor effects by diabetes status and albuminuria level

In their meta-analysis of trial data from eight randomised, double-blind, placebo-controlled trials of SGLT2 inhibitors with a CKD licence, Staplin and colleagues explored the net absolute impact on safety and efficacy, and the relative benefits on CKD, hospitalisation for any cause and mortality, stratified by diabetes status and uACR levels.

A total of 58 816 people were included in the analysis. Compared with placebo recipients, people treated with an SGLT2 inhibitor had lower rates of CKD progression, acute kidney injury, all-cause hospitalisation and all-cause mortality. Event rates were consistent in those with and without type 2 diabetes (*Table 1*).

Diabetes-specific hazard ratios were similar between those with uACR ≥200 mg/g (approximately ≥20 mg/mmol) and those with lower uACR; however, the greater absolute risk of kidney disease progression in those with higher albuminuria resulted in larger absolute benefits with SGLT2 inhibitor treatment. All subgroups had significant reductions in absolute risk.

The authors of an accompanying independent editorial agree that these two meta-analyses support the use of SGLT2 inhibitors for slowing CKD progression in all people with CKD and eGFR ≥20 mL/min/1.73 m^2, with or without type 2 diabetes and irrespective of albuminuria levels (Gregg et al, 2025). They suggest that although SGLT2 inhibitors should no longer be reserved for those with significant albuminuria at highest risk of CKD progression, this remains the group in which the drugs are likely to be most cost-effective.

Meta-analysis 3: Effects of empagliflozin versus placebo in CKD

In their meta-analysis of individual-level data in 23 340 people enrolled in four large placebo-controlled trials of empagliflozin (EMPA-REG OUTCOME, EMPEROR-Reduced, EMPEROR-Preserved and EMPA-KIDNEY), Herrington and colleagues assessed how outcomes correlated with the predicted size of initial eGFR dip and aimed to quantify SGLT2 inhibitor impact among subgroups with diabetes or heart failure, and by baseline eGFR or albuminuria.

Outcomes with empagliflozin versus placebo:

- Marker of acute kidney injury (≥50% increase in creatinine in consecutive follow-up samples): 20% lower risk.
- Acute kidney injury: 27% lower risk.
- CKD progression: 30% lower risk.
- Kidney failure: 34% lower risk.
- Chronic annual rate of eGFR decline: slowed by 64% overall (74% in those with diabetes, 47% in those without diabetes and with low albuminuria).
- On average, an initial dip in eGFR of 3.5 recovered by 2.8 mL/min/1.73 m^2 (around 80% of the initial dip), but the extent of recovery varied between individuals.

Relative benefits were similar in subgroups divided by predicted size of acute eGFR dip, and were irrespective of diabetes or heart failure status, eGFR or albuminuria levels.

Discussion

As with the previous two studies, this third meta-analysis demonstrates meaningful benefits of SGLT2 inhibitors in slowing eGFR decline even in people at lower risk, such as those without type 2 diabetes or with low albuminuria. People with lower baseline risk of progression demonstrated greater relative benefits of empagliflozin treatment versus placebo, while those at highest risk of progression had the greatest absolute benefits.

In an accompanying comment, Zoccali and Mallamaci (2025) highlight the robust reassurance provided by the meta-analysis that

the acute eGFR dip seen after SGLT2 inhibitor initiation does not reduce the long-term benefits or increase the risk of acute kidney injury; thus, there is no need to check eGFR after initiation in the majority of people. eGFR monitoring after initiation may be appropriate, however, when multiple therapies that may cause volume depletion are being co-prescribed.

All three meta-analyses confirm the value of early SGLT2 inhibitor use in those with CKD, with or without diabetes, and even in those without significant albuminuria. The eGFR dip and the variability between individuals is still incompletely understood, but it is reassuring that this does not reduce the long-term acute and chronic renal disease benefits, or increase the risk of acute kidney injury.

Implications for practice

These meta-analyses highlight the benefits of SGLT2 inhibitors even in people we may have believed to be at low risk of CKD progression or those at high risk of acute kidney injury. Currently, even in practices where we are comfortable initiating SGLT2 inhibitors and understand the huge benefits of this drug class, not all those who would benefit are receiving SGLT2 inhibitors.

Although clinical inertia is improving with education, and the PCDO Society is working hard to help with this, people with type 2 diabetes or CKD are also often reluctant to add to their medication burden. Aligning education and explanations of the benefits with what is important to people may help them to accept additional therapy. By using more combination drugs (e.g. combinations of metformin and SGLT2 inhibitors), we may be able to reduce pill burden and improve uptake and adherence.

The circulated draft of the new NICE type 2 diabetes guideline planned for publication in February 2026 proposes that all those with type 2 diabetes should be prescribed an SGLT2 inhibitor unless there is a contraindication. It is, therefore, timely not only to understand the benefits of these drugs but also to remind ourselves of the situations where they may not be suitable. Our *Prescribing pearls* guide to SGLT2 inhibitors will be useful for this.

It is hoped these studies will give us the confidence to use these drugs more widely, including in those with CKD but without type 2 diabetes, and we can be reassured that, unlike when initiating and titrating ACE inhibitors or ARBs, only carefully selected people need eGFR monitoring shortly after initiating SGLT2 inhibitors.

This may be the ideal time to review the percentage of people with type 2 diabetes or CKD already on an SGLT2 inhibitor, and set some practice targets so the benefits of these drugs can be gained more widely. ■

Gregg LP, Bozkurt B, Navaneethan SD (2025) Time for broader adoption of SGLT2 inhibitors in clinical practice? *JAMA* 7 Nov [Epub ahead of print]. https://doi.org/10.1001/jama.2025.21336

Herrington WG, Che ZJ, Sardell R et al (2025) Effects of empagliflozin on conventional and exploratory acute and chronic kidney outcomes: An individual participant-level meta-analysis. *Lancet Diabetes Endocrinol* **13**: 1003–14. https://doi.org/10.1016/s2213-8587(25)00222-0

Neuen BL, Fletcher RA, Anker SD et al; SGLT2 Inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium (SMART-C) (2025) SGLT2 inhibitors and kidney outcomes by glomerular filtration rate and albuminuria: A meta-analysis. *JAMA* 7 Nov [Epub ahead of print]. https://doi.org/10.1001/jama.2025.20834

Staplin N, Roddick AJ, Neuen BL; SGLT2 Inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium (SMART-C) (2025) Effects of sodium glucose cotransporter 2 inhibitors by diabetes status and level of albuminuria: A meta-analysis. *JAMA* 7 Nov [Epub ahead of print]. https://doi.org/10.1001/jama.2025.20835

Zoccali C, Mallamaci F (2025) Empagliflozin in chronic kidney disease: Evidence for early, inclusive, and confident use. *Lancet Diabetes Endocrinol* **13**: 988–9. https://doi.org/10.1016/s2213-8587(25)00224-4

With the number of people requiring dialysis predicted to rise fivefold in the next 10 years, what can primary care do to prevent this public health crisis?

Click the thumbnail to see the advice from the PCDO Society and UK Kidney Association.

Practice points

1. The benefits and safety profile of SGLT2 inhibitors in people with chronic kidney disease (CKD) have been demonstrated independently of diabetes or heart failure status, baseline eGFR or albuminuria level.
2. Greater benefits are obtained when these drugs are initiated early in the course of CKD.
3. There is no need to check eGFR soon after initiation of an SGLT2 inhibitor in the majority of people, unless multiple therapies that may cause volume depletion are co-prescribed.
4. This may be the ideal time for practices to audit the proportion of people with type 2 diabetes or CKD who are taking an SGLT2 inhibitor, and set targets so that more people can gain the benefits of these drugs.