DELIVERing reassurance that early eGFR reductions with SGLT2 inhibitors should not prompt drug discontinuation

A pre-specified secondary analysis of the DELIVER randomised controlled trial in 5788 people with heart failure with mildly reduced or preserved ejection fraction, with or without type 2 diabetes, explored the implications of early eGFR changes after initiation of dapagliflozin on later cardiovascular and renal risk. As expected, from baseline to 1 month, eGFR declines of >10% were more common in those actively treated with dapagliflozin than in those treated with placebo, occurring in 40% versus 25%. In placebo recipients, experiencing an initial eGFR reduction of >10% was associated with a higher risk of major adverse cardiovascular events. However, in those treated with dapagliflozin, although an initial eGFR reduction of >10% was common, this was not associated with adverse cardiovascular or renal outcomes compared to those treated with dapagliflozin who experienced smaller initial reductions in eGFR. The authors concluded that these findings reinforce the advice, based on earlier studies in those at high risk of cardiorenal disease, that SGLT2 inhibitors need not usually be discontinued or interrupted in response to an initial eGFR reduction. Other studies and editorials have concluded that routine monitoring of renal function is not required after initiating SGLT2 inhibitors unless volume depletion is considered a risk.

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When initiating or titrating an ACE inhibitor or ARB, clinicians are aware of the need to check eGFR and serum potassium levels 1–2 weeks after each dose change. Identifying alterations in these measurements may result in the need to reduce or discontinue the drug, for example if eGFR falls by ≥25% or if potassium is persistently above 5 mmol/L and not reduced by altering other medications.

SGLT2 inhibitors work by inhibiting reabsorption of sodium and glucose in the proximal tubule of the kidneys, increasing loss of fluid and glucose and decreasing intraglomerular pressure. When SGLT2 inhibitors were introduced, it was believed they might increase the risk of acute kidney injury, and this was supported by findings of an early decline in eGFR following SGLT2 inhibitor initiation. Monitoring of renal function was therefore recommended initially. It has since become clear that this initial acute, reversible decline (often called an eGFR "dip") frequently occurs but that long-term treatment with cardioprotective SGLT2 inhibitors can reduce the risk of cardiovascular events, improve heart failure symptoms and outcomes, and that all SGLT2 inhibitors slow renal disease progression.

Initially, it was unclear whether this early eGFR dip was an important safety signal or, conversely, a signal of likely cardiorenal benefit. A *post hoc* analysis of the EMPA-REG OUTCOME study in people with type 2 diabetes and cardiovascular disease (CVD) demonstrated that 28% of the empagliflozin group had eGFR reductions of >10% at 4 weeks compared with 13% of those receiving placebo, with no difference in acute kidney injury rates, safety outcomes or long-term renoprotective effects between empagliflozin recipients with or without the eGFR dip (Kraus et al, 2021). A *post hoc* analysis of the CREDENCE trial found that 45% of people treated with canagliflozin had a >10% eGFR reduction, compared with 21% of those receiving placebo (Oshima et al, 2021). However, there was no significant difference in

Citation: Brown P (2023) Diabetes Distilled: DELIVERing reassurance that early eGFR reductions with SGLT2 inhibitors should not prompt drug discontinuation. *Diabetes & Primary Care* **25**: [Early view publication]

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long-term renal protection between dippers and non-dippers, apart from in the 0.5% treated with canagliflozin who had a >30% initial eGFR drop; this small group had a slightly increased risk of kidney-related adverse events.

Significant clinical inertia regarding initiation of SGLT2 inhibitors persists amongst primary care teams, despite guideline recommendations to prescribe these drugs as joint initial therapy in people with established CVD, heart failure or chronic kidney disease (irrespective of the presence of type 2 diabetes in the latter two conditions), and to consider them in those at high risk of CVD. In discussions with clinicians in primary care who are disinclined to initiate, there is reluctance due to these being new drugs, ongoing uncertainty relating to eGFR testing and management of results, as well as feeling underskilled to deliver detailed pre-initiation discussion of the possible side effects and the importance of pausing the SGLT2 inhibitor and metformin when unwell and at risk of fluid depletion.

The present study

In this pre-specified *post hoc* analysis of the DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) randomised controlled trial, published in *JAMA Cardiology*, Mc Causland and colleagues explored the implications of early eGFR changes following dapagliflozin initiation on later cardiovascular and renal risk. The participants were aged ≥40 years with symptomatic heart failure with mildly reduced or preserved ejection fraction (ejection fraction >40%), and were randomised to treatment with dapagliflozin 10 mg or placebo. The primary outcome was the composite of cardiovascular death or worsening heart failure, and the *post hoc* kidney outcome was a composite of a ≥50% eGFR reduction relative to month 1, development of end-stage renal disease, eGFR <15 mL/min/1.73 m^2 or death due to renal causes.

Results

In the first month of treatment, 42% of participants had no decline in eGFR, 26% had a 0–10% decline and 32% had a >10% decline. Those with eGFR decline >10% were slightly older (72 vs 71 years) and had very slightly higher systolic blood pressure (129 vs 128 mmHg). The median change in eGFR over the first month was –4% in those on dapagliflozin versus –1% in those on placebo, and 40% of those receiving dapagliflozin had eGFR reductions >10% in the first month compared to 25% of those receiving placebo. Further analysis of the dapagliflozin group demonstrated that an eGFR reduction of >10% was more common in those with initial eGFR ≤60 mL/min/1.73 m^2, those not taking an ACE inhibitor or ARB, and those not on a mineralocorticoid receptor antagonist at baseline.

Over the study follow-up, in the placebo group, the primary cardiovascular outcome was significantly more common in those with an initial eGFR reduction of >10% compared to those without (adjusted hazard ratio 1.33). In contrast, there was no significant difference in risk between dapagliflozin recipients who had a >10% eGFR dip and those who did not.

Likewise, in those assigned to placebo, the *post hoc* kidney outcome occurred more commonly in those with an initial eGFR drop of >10% compared to those with a lower initial eGFR decline (2.3% vs 1.8%). The adjusted hazard ratio was 1.62, although the 95% confidence interval was 0.90–2.89 and this was not statistically significant. In those treated with dapagliflozin, the kidney outcome occurred in only 1.3%, with no difference between the eGFR dip subgroups.

Discussion

This study demonstrated that, although an initial decline in eGFR of >10% was more common in the first 4 weeks after initiation in those treated with dapagliflozin, this was not associated with a higher risk of cardiovascular outcomes or any difference in longer-term eGFR decline compared with dapagliflozin recipients who experienced lower initial eGFR declines. Other studies have demonstrated that the initial acute decline is not associated with evidence of kidney damage.

This was a pre-specified, secondary analysis from a well-executed randomised clinical study involving a large number of participants. It looked only at those with heart failure with mildly

reduced or preserved ejection fraction (with and without type 2 diabetes), but other studies in other groups treated with dapagliflozin, and in those treated with other SGLT2 inhibitors, have been similarly reassuring.

This and other similar evaluations reinforce recommendations that routine eGFR testing is not required after SGLT2 inhibitor initiation, unless volume depletion is suspected (e.g. blood pressure <120/70 mmHg, orthostatic symptoms, in people taking high-dose diuretics and, possibly, in the elderly) (Heerspink and Cherney, 2021). Since SGLT2 inhibitors do not cause potassium increases like ACE inhibitors or ARBs, there is no need to measure this routinely, except when required for other drugs.

Cardioprotective SGLT2 inhibitors are now known to provide significant reductions in cardiovascular risk, symptomatic improvement, and reductions in hospitalisation and other outcomes in people with all types of heart failure, and all SGLT2 inhibitors have demonstrated a slowing of renal disease progression. Now that the uncertainty about early reductions in eGFR is resolved, we owe it to our patients to upskill ourselves in the use of SGLT2 inhibitors using the resources in this journal (including a How to guide and a Need to know list of the licensed indications and doses) so that we can safely provide these significant benefits to the people we care for.

Let's make 2024 the year we implement guideline recommendations and help more people make an informed choice to take SGLT2 inhibitors! ■

Heerspink HJL, Cherney DZI (2021) Clinical implications of an acute dip in eGFR after SGLT2 inhibitor initiation. *Clin J Am Soc Nephrol* **16**: 1278–80

Kraus BJ, Weir MR, Bakris GL et al (2021) Characterization and implications of the initial estimated glomerular filtration rate "dip" upon sodium–glucose cotransporter-2 inhibition with empagliflozin in the EMPA-REG OUTCOME trial. *Kidney Int* **99**: 750–62

Oshima M, Jardine MJ, Agarwal R et al (2021) Insights from CREDENCE trial indicate an acute drop in estimated glomerular filtration rate during treatment with canagliflozin with implications for clinical practice. *Kidney Int* **99**: 999–1009

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