

# Cardio-renal protection with empagliflozin

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**Abstract:** Cardiovascular (CV) and kidney disease are common and significant complications in people with type 2 diabetes (T2DM). CV disease is the leading cause of death, morbidity and hospitalisations for people with T2DM. Furthermore, diabetic kidney disease is a major risk factor for CV disease and is the main reason why patients need renal replacement therapy. In this perspective, we highlight the results of the recent landmark EMPA-REG OUTCOME trial which has shown that empagliflozin, a member of the sodium-glucose co-transporter 2 (SGLT-2) inhibitor class of glucose lowering medications, reduces death from CV causes, hospitalisation for heart failure and progression to end stage kidney disease in patients with T2DM and established CV disease. The SGLT2 receptor mediates high-capacity glucose uptake in the early proximal tubule, and SGLT2 inhibitors, via their ability to promote glycosuria, have been developed as glucose lowering medications. As well as having a glucose lowering effect, SGLT-2 inhibitors also reduce blood pressure, promote weight loss and reduce uric acid levels. Potential side-effects or concerns related to the use of SGLT-2 inhibitors include increased rates of urinary tract infections, genital tract infections, postural hypotension, diabetic ketoacidosis, acute kidney injury and possible increased rates of fractures. The exact mechanisms that result in empagliflozin's dramatic CV and renal protective effects, with a very favourable safety/tolerability profile, in the EMPA-REG study remain to be fully defined. However, they are most likely distinct from the glucose lowering effects of empagliflozin. CV safety trials involving dapagliflozin and canagliflozin, members of the SGLT-2 class, are under way and the results from these studies will help to answer the question as to whether the cardio-renal benefits of empagliflozin are a class-effect or not. Without doubt, trials to investigate whether SGLT-2 inhibitors have cardio-renal protective effects in patients without diabetes will start soon.

**Keywords:** Empagliflozin; SGLT-2 inhibitors; diabetes; cardiovascular disease; diabetic kidney disease

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Patients with type 2 diabetes (T2DM) are at high risk for the development of cardiovascular (CV) and renal disease. Heart failure is an adverse CV outcome whose association with diabetes is being increasingly recognised (1). Prevalence rates for heart failure in people with diabetes have been reported to range between 10% to 20% and the incidence rate is approximately 2.5 times that in people without diabetes (2-4). The finding of heart failure and diabetes is not only common but also associated with a very poor prognosis. The median survival of patients with these dual pathologies is reported to be around 4 years (5). The relationship between diabetes and heart failure has also been complicated by reports of some glucose-lowering agents, in particular the thiazolidinediones

and some inhibitors of dipeptidyl peptidase 4 (DDP-4), being associated with an increased risk for the development of heart failure (6). Given the above, it is timely to highlight the results of the landmark EMPA-REG OUTCOME trial which has shown that empagliflozin, a member of the sodium-glucose co-transporter 2 (SGLT-2) inhibitor class of glucose lowering medications, reduces death from CV causes, hospitalisation for heart failure and progression to end stage kidney disease (ESKD) in patients with T2DM and established CV disease (7).

The SGLT2 receptor mediates high-capacity glucose uptake in the early proximal tubule, and SGLT2 inhibitors, via their ability to promote glycosuria, have been developed

as glucose lowering medications. As well as having a glucose lowering effect, SGLT-2 inhibitors also reduce blood pressure, promote weight loss and reduce uric acid levels (8,9). The main disadvantage of the mode of action of the SGLT-2 inhibitors is that their effectiveness for lowering blood glucose levels is dependent on renal function (10). Hence they are not recommended as glycaemic management agents in patients with impaired renal function. Potential side-effects or concerns related to the use of SGLT-2 inhibitors include increased rates of urinary tract infections, genital tract infections, postural hypotension, diabetic ketoacidosis, acute kidney injury and possible increased rates of fractures (8,10,11).

In the landmark CV safety trial of empagliflozin (EMPA-REG OUTCOME trial), 7020 T2DM patients at high risk for CV events were randomised to receive empagliflozin (with no differences seen for 10 or 25 mg doses) versus placebo (7). In the combined pool of participants who received 10 mg or 25mg of empagliflozin, there was a reduction in the risk of development of CV and all-cause mortality when compared with placebo over 3.1 years. The primary composite outcome of the trial, death from CV causes, nonfatal myocardial infarction, or nonfatal stroke, occurred in 10.5% of empagliflozin and 12.1% of placebo treated patients [hazard ratio (HR) =0.86%; 95% confidence intervals (CI): 0.72–0.99]. There were no significant differences between empagliflozin and placebo treated patients for rates of nonfatal myocardial infarction or stroke, indicating that the reduction in the primary end-point in empagliflozin treated patients was mainly accounted for by lower rates of death from CV causes (HR =0.62; 95% CI: 0.49–0.77,  $P<0.001$ ). Other important benefits seen in empagliflozin treated patients included reductions in rates for hospitalization for heart failure (HR =0.65; 95% CI: 0.5–0.85,  $P=0.002$ ) and death from any cause (HR =0.68; 95% CI: 0.57–0.82,  $P<0.001$ ).

In a follow-up study that focused on heart failure outcomes in EMPA-REG, empagliflozin versus placebo treated patients had significantly lower risks of hospitalisation for heart failure or CV death (HR=0.66; 95% CI: 0.55–0.79,  $P<0.001$ ), hospitalisation for or death from heart failure (HR=0.61; 95% CI: 0.47–0.79,  $P<0.001$ ) and all-cause hospitalisation (HR =0.89; 95% CI: 0.82–0.96,  $P=0.003$ ) (12). The risk in the primary endpoint and the heart failure outcomes in empagliflozin treated patients reported in EMPA-REG were consistently lower in subgroup analysis exploring the effects of age, renal function, use of blockers of the renin-angiotensin system,

lipid lowering medications, diuretics and the presence or absence of heart failure at baseline. However, in the smaller number of patients who did have heart failure at baseline (approximately 10%), rates of hospitalisation for heart failure for empagliflozin versus placebo treated patients just failed to reach statistical significance (HR=0.75; 95% CI: 0.48–1.19).

Furthermore, another follow up study from EMPA-REG has shown that empagliflozin leads to an improvement in renal outcomes (13). The primary renal end point of the trial was a four point composite of new onset or worsening of nephropathy (progression to macroalbuminuria, doubling of serum creatinine level associated with an estimated glomerular filtration rate (eGFR)  $<45$  mL/min/1.73 m<sup>2</sup>, initiation of renal replacement therapy and death from renal disease). This endpoint occurred in 18.8% of placebo and 12.7% of empagliflozin treated patients (again with no differences seen for 10 or 25 mg doses) which resulted in a risk reduction of 39% in patients that received empagliflozin (HR =0.61; 95% CI: 0.53–0.7,  $P<0.001$ ).

The main driver for a reduction in the primary renal endpoint in empagliflozin treated patients was a slowing in progression to macroalbuminuria, 16.2% *vs.* 11.2% in placebo and empagliflozin treated patients, respectively (HR =0.62; 95% CI: 0.54–0.72,  $P<0.001$ ). A number of sensitivity analyses were therefore performed to test the strength of the relationship between empagliflozin treatment and the reduction in clinically meaningful renal endpoints. Of note, empagliflozin versus placebo treatment resulted in a 46% risk reduction in the composite renal endpoint of doubling of serum creatinine levels (plus in this study achieving an eGFR  $<45$  mL/min/1.73 m<sup>2</sup>), initiation of renal replacement therapy and death from renal disease (HR =0.54; 95% CI: 0.40–0.75,  $P<0.001$ ).

The mechanisms explaining the improved cardio-renal outcomes in EMPA-REG for empagliflozin treated patients remain to be fully defined. Although empagliflozin modestly improved HbA1c levels, systolic blood pressure, weight, waist circumference and uric acid levels during the trial, other mechanisms are most likely responsible for the early appearance of the impressive cardio-renal protective effects of empagliflozin (7,12,13).

SGLT-2 inhibitors cause volume contraction from a sustained osmotic diuresis and natriuresis which could potentially play a prominent role in explaining the improved heart failure outcomes in EMPA-REG (9). Other proposed mechanisms include a shift in cardiac fuel metabolism from fat and glucose oxidation to ketone bodies

in empagliflozin treated patients (14,15). SGLT-2 inhibitors are known to increase ketone levels in the circulation and their use has been associated with the development of diabetic ketoacidosis (16). The mechanisms linking SGLT-2 inhibitors with increased circulating ketone body levels is not fully understood but may relate to alterations in the insulin to glucagon ratio and a decrease in the renal clearance of ketones bodies. As opposed to glucose or free fatty acids, ketones bodies are known to provide a more fuel efficient substrate for energy production which improves myocardial and most likely renal work efficiency and function (14,15). However, further mechanistic studies are warranted to test this hypothesis.

The mechanisms that result in the renal protective effects of empagliflozin may also relate to an alteration in intra-renal haemodynamics. In empagliflozin treated patients in EMPA-REG there was an initial drop in eGFR and a rapid increase in eGFR values after discontinuation of the medication (13). These findings would be consistent with a direct effect of the empagliflozin on renal haemodynamics effecting blood flow and pressure in the glomerulus. In hyperfiltering patients with type 1 diabetes, empagliflozin has been shown to reduce GFR and resolve hyperfiltration in short term studies by modulating tubulo-glomerular feedback mechanisms (17). Specifically, SGLT-2 inhibitors are known to constrict the afferent glomerular arteriole in response to an increase in tubular sodium sensed by the macula densa in the distal tubule. This increase in tubular sodium results from less sodium being reabsorbed in the proximal tubule due to inhibition of sodium-glucose co-transport (17-19).

Although there is no ability to directly measure intra-glomerular pressure in humans, it is hypothesised that there is a reduction in intraglomerular pressure ultimately results in a preservation of GFR. Improved cardiac function and the avoidance of heart failure are also possible mechanism that indirectly contribute to the improved renal outcomes in patients treated with empagliflozin in EMPA-REG.

From a safety point of view, rates of ketosis, events related to volume depletion, fractures and acute kidney injury were not greater in empagliflozin versus placebo treated patients in EMPA-REG (7,13). Unexpectedly, rates of acute injury were less in empagliflozin versus placebo treated patients. This is a reassuring finding as approximately 80% of patients in EMPA-REG were taking blockers of the renin angiotensin system, which are also known to decrease intra-glomerular pressure. Consistent

with the expected side-effect profile of SGLT-2 inhibitors, rates of genital tract infections were higher in empagliflozin versus placebo treated patients (6.4% *vs.* 1.8%, respectively,  $P < 0.05$ ) (7).

In summary, SGLT-2 inhibitors improve HbA1c levels when added to metformin without causing hypoglycaemia. They also have the advantages of promoting weight loss and lower blood pressure. A member of this drug class, empagliflozin, has recently been shown offer cardio-renal protection in high risk vascular patients with type 2 diabetes. CV safety trials involving dapagliflozin and canagliflozin are under way and the results from these studies will help to answer the question as to whether the cardio-renal benefits of empagliflozin are a class-effect or not (20). Without doubt, trials to investigate whether SGLT-2 inhibitors have cardio-renal protective effects in patients without diabetes will start soon.

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## Footnote

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