A RESEARCH REVIEW™
STUDY REVIEW

Consistent effects of empagliflozin on cardiovascular and kidney outcomes irrespective of diabetic kidney disease categories: Insights from the EMPA-REG OUTCOME trial

Making Education Easy 2022

About the Expert

Ryan G Paul
BHB, MBChB (Auckland), FRACP, PhD

Ryan Paul is an endocrinologist and diabetologist at the Waikato DHB and in private practice in Hamilton. Ryan is active in research in his roles as a Senior Lecturer at the University of Waikato and as an Honorary Lecturer at the University of Auckland. He has key roles in teaching Primary Care and Diabetes Nurse Prescribers in New Zealand and is a member of the RACP New Zealand Adult Medicine Committee. Ryan is the immediate Past President of the New Zealand Society of Endocrinology (NZSE) and is a current Executive Member of the NZSSD. In 2019, he was awarded Clinical Educator of the Year by the New Zealand Medical Council.

Abbreviations used in this review
ACE = angiotensin-converting enzyme
ARB = angiotensin receptor blocker
CKD = chronic kidney disease
CVD = cardiovascular disease
DKD = diabetic kidney disease
eGFR = estimated glomerular filtration rate
HbA1c = haemoglobin A1c
HHF = hospitalisation for heart failure
MACE = major adverse cardiovascular events
MI = myocardial infarction
SGLT-2 = sodium-glucose contransporter-2
T2D = type 2 diabetes
uACR = urinary albumin-to-creatinine ratio

ABOUT RESEARCH REVIEW

Research Review is an independent medical publisher producing electronic publications in a wide variety of specialist areas. Content is created independently of sponsor companies with assistance from leading specialists. Study Reviews summarise a key clinical paper with independent expert oversight and commentary.

SUBSCRIBE AT NO COST TO ANY RESEARCH REVIEW

NZ health professionals can subscribe to or download previous editions of Research Review publications at www.researchreview.co.nz

RESEARCH REVIEW™
Making Education Easy — Since 2006

Diabetes is the leading cause of kidney failure. Additionally, elevated albuminuria predicts increased cardiovascular and renal risk. This publication summarises a post hoc analysis of the EMPA-REG OUTCOME trial examining the cardiovascular and kidney effects of empagliflozin in patients with different clinical phenotypes of diabetic kidney disease (DKD) as approximately one-third of patients had DKD at study entry. This review is sponsored by Boehringer Ingelheim and Eli Lilly.

A free full-text PDF of the paper *Consistent effects of empagliflozin on cardiovascular and kidney outcomes irrespective of diabetic kidney disease categories: Insights from the EMPA-REG OUTCOME trial.* Diabetes Obes Metab. 2020;22(12):2335-2347 is available here.

EMPA-REG OUTCOME was a double-blind, placebo-controlled, multinational trial that randomised T2D patients with an HbA1c of 7-10% (53-86 mmol/mol) and established CVD to the SGLT-2 inhibitor empagliflozin (10 mg or 25 mg) or placebo (1:1:1), in addition to standard care. Kidney function inclusion criteria was an eGFR ≥ 30 mL/min/1.73m^2, regardless of the presence or absence of albuminuria at baseline.

This study by Wanner *et al* compared the treatment effects of empagliflozin (10 mg and 25 mg) versus placebo on the cardiovascular and kidney outcomes for 7020 patients from EMPA-REG OUTCOME. The investigators stratified patients at baseline into three groups according to the presence or absence of overt albuminuria:

1. Overt DKD – 769 patients (uACR > 34 mg/mmol with any eGFR)
2. Non-overt DKD – 1290 patients (uACR ≤ 34 mg/mmol and eGFR < 60 mL/min/1.73m^2)
3. All other patients – 4893 patients (uACR ≤ 34 mg/mmol and eGFR ≥ 60 mL/min/1.73m^2)

The median duration of treatment was 2.6 years, 97% of patients completed the study and the median observation time was 3.1 years. More than 90% of patients were taking antihypertensives; an ACE inhibitor or an ARB in > 80% of cases with similar frequencies across subgroups.

The CV outcomes for the study were CV death, hospitalisation for heart failure (HFF), the composite of HHF or CV death (excluding fatal stroke), all-cause hospitalisation, all-cause mortality and three-point MACE. The primary kidney outcome was incident or worsening nephropathy defined as progression to macroalbuminuria, initiation of kidney replacement therapy or death from kidney disease. Two *post hoc* renal endpoints were also included. Firstly, a "hard" endpoint defined as initiation of kidney replacement therapy, a sustained eGFR < 15 mL/min/1.73m^2, a sustained doubling of serum creatinine from baseline or kidney death. Secondly, an "alternative" kidney endpoint defined as eGFR < 10 mL/min/1.73m^2, a sustained 40% decline in eGFR from baseline, initiation of kidney replacement or kidney death. Patients with overt DKD were not considered for the endpoint of incident or worsening nephropathy.

Empagliflozin significantly reduced the risk of CV death, HHF, and all-cause hospitalisation for all three subgroups of the trial population (**Figure 1**; all p values for interaction <0.05). Empagliflozin had no effect on MI or stroke across the three subgroups.

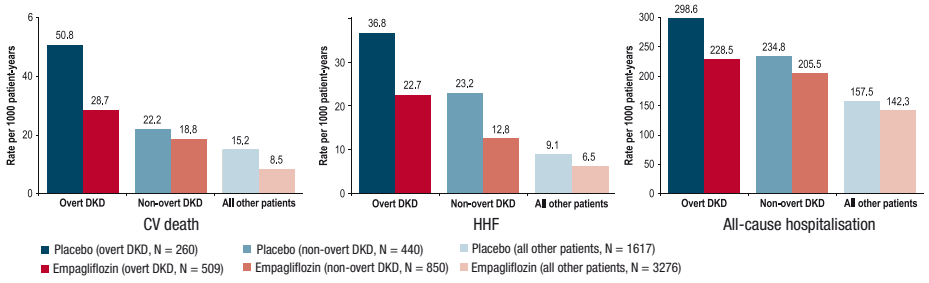

Figure 1: Incidence rates for CV outcomes for patients with T2D from EMPA-REG OUTCOME stratified by albuminuria levels and treated with empagliflozin or placebo.

Empagliflozin significantly reduced the risk of incident or worsening nephropathy, the hard composite endpoint and the alternative kidney composite endpoint for all three subgroups of the trial population (**Figure 2**; all p values for interaction <0.05). Similar results were seen when CV death was added to each of the three composite kidney endpoints. Importantly, empagliflozin also significantly reduced the annual decline in eGFR across all three subgroups as assessed by annual mean eGFR slopes (p<0.001 for all within-group comparisons).

The safety profile of empagliflozin was similar across all patient subgroups. The rate of genital infection was higher in all groups taking empagliflozin, compared to placebo. All other adverse effects in patients taking empagliflozin occurred at rates similar or lower than placebo.

Helping New Zealand health professionals keep up to date with clinical research

Consistent effects of empagliflozin on cardiovascular and kidney outcomes irrespective of diabetic kidney disease categories: Insights from the EMPA-REG OUTCOME trial

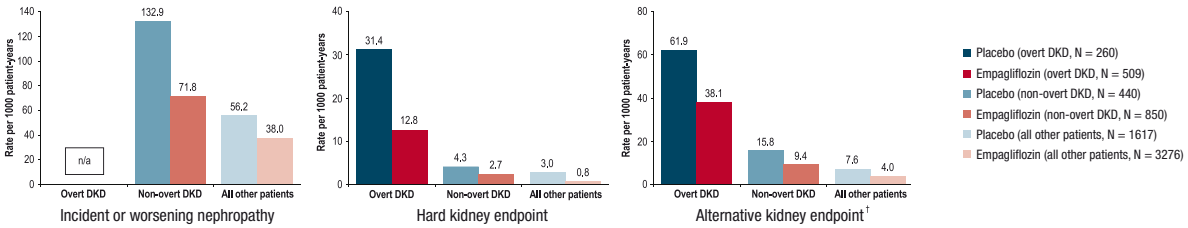

Figure 2: Incidence rates for renal outcomes for patients with T2D from EMPA-REG OUTCOME stratified by albuminuria levels and treated with empagliflozin or placebo.

The study results suggest that in addition to standard care, empagliflozin improves CV and renal outcomes and slows the progression of kidney disease in patients with T2D, irrespective of the presence or absence of albuminuria. This result is important because non-overt DKD appears to be increasing in prevalence and previous studies have largely focussed on the benefits of SGLT-2 inhibitors in patients with overt DKD. The authors noted, however, that the inclusion criteria of established CVD and an eGFR ≥ 30 mL/min/1.73m^2 may limit the generalisability of this study. The observation that treatment effects were consistent across all three patient subgroups led the investigators to speculate that SGLT-2 inhibitors may provide cardio/renal benefits in T2D beyond that thought to be provided by the lowering of intra-glomerular pressure.

EXPERT COMMENTARY

Over two-thirds of patients with T2D in Aotearoa New Zealand will die from CV and/or renal disease and these rates are significantly higher in Māori and Pacific peoples. Importantly, over one-third of New Zealanders with T2D already have renal or CV disease, or the equivalent CV risk, and interventions are required to prevent progression to early CV or renal death. This is highly relevant given that the earlier death of Māori and Pacific peoples with diabetes has not changed in the past 20 years and we had the welcome but overdue arrival of empagliflozin and dulaglutide to Aotearoa last year.

This sub-analysis by Wanner and colleagues of the pivotal EMPA-REG OUTCOME trial highlights that empagliflozin will likely reduce morbidity and mortality in all patients with diabetes with CV and/or renal disease. Further, these benefits occur despite only moderately suboptimal glycaemic control and are additional to the benefits of blockade of the renin-angiotensin system by ACE inhibitors and ARBs. Notably, these CV benefits are seen within weeks and occur regardless of the dose of empagliflozin and the severity of CVD.[1–3] Similarly, this sub-analysis shows that the CV and renal benefits of empagliflozin occur at all levels of severity of renal disease >30 mL/min/m^2.

The traditional diabetic renal disease dogma of microalbuminuria progressing to macroalbuminuria and then declining renal function does not fit all patients. Indeed, diabetic renal disease is now recognised as being more heterogenous and can be evident by any degree of albuminuria and/or reduced eGFR. So, in addition to empagliflozin being effective at all levels of renal dysfunction (>30 mL/min/m^2), this sub-analysis shows that empagliflozin is effective independently of the degree of albuminuria. Although the glucose-lowering effects of empagliflozin reduce with declining renal function, this sub-analysis reveals that empagliflozin still decreases the need for renal replacement therapy and renal death in those with an eGFR between 30 to 60 mL/min. Conversely, unlike empagliflozin, dualglutide is yet to be shown to prevent the need for renal replacement, renal death or heart failure. This is because unlike worldwide, prescribers in Aotearoa New Zealand are forced to choose between funded empagliflozin or dulaglutide. Consequently, empagliflozin is likely the best choice for those where renal disease and/or heart failure predominates. But it is important to remember that empagliflozin is still at least a second-line agent after lifestyle management and metformin, and it is yet to be definitively shown to prevent renal disease.

It is important to note that the EMPA-REG OUTCOME trial was primarily designed as a CV safety trial and secondarily to detect any benefits on composite CV outcomes. Although empagliflozin did not reduce MI in this sub-analysis, empagliflozin and the other SGLT-2 inhibitors have been consistently and clearly shown to reduce the risk of MI in those with known CVD in other studies. However, unlike dulaglutide, these studies confirm that SGLT-2 inhibitors do not appear to reduce the risk of stroke. The finding that the only safety concern with empagliflozin was the increased risk of genital infection, which were primarily mycotic infections such as vaginal thrush or balanitis, highlights the importance of discussing genital hygiene when using empagliflozin. Current guidance recommends women wash their genital area at least twice per day and uncircumscribed men at least once a day, and cautious use of empagliflozin if previous frequent or severe genital infections.

The mechanisms of how empagliflozin leads to its impressive CV benefits are not well characterised, but as the authors suggest, appear to be additional to lowering of intra-glomerular pressure. As discussed, the benefits are also independent of effects on glucose levels and the rapid onset suggests that reduced atherosclerotic disease is not a major mechanism. Proposed alternative mechanisms include decreased afterload from diuresis and reduced blood pressure, and reductions in cardiac inflammation, uric acid levels, sympathetic nervous activity and oxidative stress. Improved vascular function and increased erythropoiesis have also been proposed as alternative mechanisms. Regardless, SGLT-2 inhibitors are set to become one of the four pillars of the pharmacological management of diabetic and non-diabetic HF alongside beta blockers, ACE inhibitors/ARBs and aldosterone blockade.

Finally, the findings of this sub-analysis were incorporated into the New Zealand Society for the Study of Diabetes (NZSSD)/Ministry of Health national guidance on the management of T2D. The key 'take home' messages for everyday practice from this sub-analysis and the guidance is that unless contraindicated, all patients with T2D with renal disease (uACR > 3 mg/mmol and/or eGFR < 60 mL/min) OR CV disease OR 5-year CV risk ≥ 15% should be on empagliflozin or dulaglutide regardless of glycaemic control; AND empagliflozin is preferable when renal disease or heart failure predominates. Moreover, empagliflozin is additional to traditional management with lifestyle improvement, metformin, ACE inhibitor/ARB and statin therapy, which remain as important as ever. There is a mismatch with the Pharmac Special Authority Criteria which requires an HbA1c > 53 mmol/mol for at least three months for funded empagliflozin, so self-funding of empagliflozin should be discussed with patients that do not meet the Special Authority criteria, when clinically appropriate. There is no evidence to date that empagliflozin is more or less effective in Māori or Pacific peoples but ensuring use of empagliflozin in Māori or Pacific peoples with T2D and renal and/or CV disease may finally lead to some progress in preventing their early death.

REFERENCES

1. McGuire DK, et al. Effects of empagliflozin on first and recurrent clinical events in patients with type 2 diabetes and atherosclerotic cardiovascular disease: a secondary analysis of the EMPA-REG OUTCOME trial. *Lancet Diabetes Endocrinol.* 2020;8(12):949-959.
2. Odutayo A, et al. Sodium-Glucose Cotransporter 2 Inhibitors, All-Cause Mortality, and Cardiovascular Outcomes in Adults with Type 2 Diabetes: A Bayesian Meta-Analysis and Meta-Regression. *J Am Heart Assoc.* 2021;10(18):e019918.
3. Verma S, et al. Time to cardiovascular benefits of empagliflozin: a post hoc observation from the EMPA-REG OUTCOME trial. *ESC Heart Fail.* 2021;8(4):2603-2607.

Boehringer Ingelheim

This article was commissioned by Boehringer Ingelheim (NZ) Ltd and Eli Lilly (NZ) Ltd. The content is entirely independent and based on studies and the author's opinion. The views expressed do not necessarily reflect the views of Boehringer Ingelheim and Eli Lilly. Before prescribing any prescription medications mentioned in this article please consult the full data sheet. Treatment decisions based on these data are the full responsibility of the prescribing healthcare professional.

Lilly

© 2022 RESEARCH REVIEW