Empagliflozin in Patients with Chronic Kidney Disease - The EMPA-KIDNEY Trial

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<tr><th colspan="3">BACKGROUND AND OVERVIEW</th></tr>
<tr><td>Article Citation</td><td colspan="2">The EMPA-KIDNEY Collaborative Group, Herrington, W. G., et. al. (2023). Empagliflozin in Patients with Chronic Kidney Disease. The New England journal of medicine, 388(2), 117–127. https://doi.org/10.1056/NEJMoa2204233</td></tr>
<tr><td>Background</td><td colspan="2">Chronic kidney disease (CKD) is a progressively debilitating disease. Glomerular filtration rate (GFR) decreases, albuminuria increases, and slowly patients progress to kidney failure, possibly requiring dialysis or kidney transplant. Renin-angiotensin system (RAS) inhibitors are commonly used for their benefit in patients with CKD, however there are not many other options to prevent CKD progression.[1]
SGLT2 inhibitors have shown benefit for patients with diabetes and underlying CKD in previous trials.[2,3,4] It has been postulated that they may have benefit for patients with CKD apart from diabetes due to subgroup analyses from the results of these trials. The goal of the EMPA-KIDNEY trial was to determine if the benefit of empagliflozin in CKD is solely in patients with diabetes or if that benefit applies in other patients as well.</td></tr>
<tr><td>Funding</td><td colspan="2">Boehringer Ingelheim provided the funding for the trial. A steering committee with members of the company, from the central coordinating office at the University of Oxford, and other clinical and statistical experts were responsible for the design and manuscript publication.</td></tr>
<tr><td>Study Objective</td><td colspan="2">The objective of this study was to evaluate the effect of empagliflozin on the progression of kidney disease and cardiovascular (CV) disease and to examine the safety profile of the drug in a wide range of patients with CKD.</td></tr>
<tr><th colspan="3">METHODS</th></tr>
<tr><td>Study Design</td><td colspan="2">● International, randomized, parallel-group, double-blind, placebo-controlled, clinical trial
● Patients entered a pre-randomization run-in phase where they received a 15-week supply of daily placebo tablets. Patients were randomized after 6 weeks of this run-in phase to either empagliflozin 10 mg daily or placebo. There was a median of 2 years of follow up.
● Blood and urine specimens were obtained for laboratory testing after at least 6 weeks of the run-in phase, and then at each follow up visit afterward
● Clinical responsibility for the patients remained with their local physicians</td></tr>
<tr><td rowspan="2">Patient Criteria</td><td>Inclusion:</td><td>Exclusion:</td></tr>
<tr><td>● Adult patients with eGFR between 20 and 45 ml/min/1.73 m^2 or eGFR of 45-90 ml/min/1.73 m^2 with a UACR of >200
● On clinically appropriate dose of a RAS inhibitor unless an investigator judged that it would not be appropriate</td><td>● Patients with polycystic kidney disease
● Patients who had received kidney transplant</td></tr>
<tr><td>Outcomes</td><td colspan="2">● Primary endpoint: progression of kidney disease (defined as end-stage kidney disease, a sustained decrease in eGFR to <10 ml per minute per 1.72 m^2, a sustained decrease in eGFR of >= 40% from baseline, or death from renal causes) or death from cardiovascular causes
● Secondary endpoints:
○ Composite of hospitalization for heart failure or death from cardiovascular causes
○ Death from any cause</td></tr>
<tr><td>Statistics</td><td colspan="2">● Primary analysis was performed using Cox-proportional hazards regression model, adjusted for baseline variables
● Power estimation: 1070 patients needed for 90% power
● Two-sided alpha of 5%, p-value <0.05 indicated statistical significance
● All analysis conducted according to the intention to treat principle</td></tr>
<tr><th colspan="3">RESULTS</th></tr>
<tr><td>Baseline Characteristics</td><td colspan="2">● Baseline characteristics were well matched
● Urinary albumin to creatinine ratio was >300 in ~51% of patients, and ~85% of patients were already on therapy with a RAAS agent
● Diabetic kidney disease was the cause of kidney dysfunction in ~31% of patients</td></tr>
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<tr><td>Outcome Summary</td><td>
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<tr><th>Outcome</th><th>Empagliflozin (n=3304)</th><th>Placebo (n=3305)</th><th>Difference</th><th>p-value</th></tr>
<tr><td>Primary: progression of CKD or death from CV causes</td><td>432 (13.1%)</td><td>558 (16.9%)</td><td>3.8% (95% CI, 0.64-0.82)</td><td><0.001</td></tr>
<tr><td>Hospitalization for HF or death from CV causes</td><td>131 (4.0%)</td><td>152 (4.6%)</td><td>0.6% (95% CI, 0.67 to 1/07)</td><td>0.15</td></tr>
<tr><td>Death from any cause</td><td>148 (4.5%)</td><td>167 (5.1%)</td><td>0.6% (95% CI, 0.70-1.08)</td><td>0.21</td></tr>
<tr><td>Serious urinary tract infection</td><td>52 (1.6%)</td><td>54 (1.6%)</td><td>0 (95% CI, 0.64-1.37)</td><td>—</td></tr>
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Summary: the primary outcome was statistically significant showing that empagliflozin reduced the progression of CKD or incidence of death from CV causes. Safety outcomes and adverse events were similar between the two groups.
NNT = 27 patients treated for 2 years for the prevention of CKD progression or death from CV causes.
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<tr><td colspan="2">DISCUSSION</td></tr>
<tr><td>Authors' Main Points in the Discussion</td><td>

Risk of progression of CKD or death from cardiovascular causes was 28% lower in the empagliflozin group than in the placebo group without major safety concerns
Treatment was effective regardless of the presence of diabetes
Risk of hospitalization for any cause was 14% lower in the empagliflozin group than in the placebo group
The results of this trial are similar to the results of similar trials with other drugs of this class, CREDENCE (canagliflozin) and DAPA-CKD (dapagliflozin)

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<tr><td>Strengths</td><td>

The trial had a large sample size and broad eligibility criteria, reflecting the population that presents with CKD
There was a high level of adherence to the trial regimen, most likely due to the run in phase, and almost complete follow up with all patients
The trial participants were well matched and distributed between different levels of CKD
In addition, only ~50% of the trial participants were diabetic, thus showing the benefit of empagliflozin in patients with CKD alone

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<tr><td>Limitations</td><td>

There were a lower than expected number of primary outcome events in the trial despite the large sample size, weakening the power estimation
Out of the patients included in the study, around 85% were already on therapy with a RAAS agent, which has shown benefit in CKD. This may have contributed to the positive results or skewed the data
Boehringer Ingelheim provided the funding for this trial and participated in the steering committee, which could have introduced bias into the trial results

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<tr><td>Personal Conclusions</td><td>Empagliflozin has already been shown to have benefit for cardiovascular and renal outcomes in patients with diabetes, and now the EMPA-KIDNEY study shows that these benefits are independent of having diabetes. In addition, the adverse effects noted with empagliflozin in this trial were similar to those reported in the placebo group. The NNT of 27 patients with CKD taking empagliflozin for 2 years to prevent one outcome of progression of kidney disease or death from cardiovascular causes is compelling. My conclusion from this study is that empagliflozin is an attractive option for patients with CKD in order to prevent disease progression and CV death. As a result of this trial I will recommend starting empagliflozin for patients with CKD to prevent progression of disease.</td></tr>
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References:

1. The EMPA-KIDNEY Collaborative Group, Herrington, W. G., et. al. (2023). Empagliflozin in Patients with Chronic Kidney Disease. *The New England journal of medicine*, *388*(2), 117–127. https://doi.org/10.1056/NEJMoa2204233
2. Nuffield Department of Population Health Renal Studies Group, & SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium (2022). Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet (London, England), 400(10365), 1788–1801. https://doi.org/10.1016/S0140-6736(22)02074-8
3. Perkovic, V., Jardine, M. J., Neal, B., Bompoint, S., Heerspink, H. J. L., Charytan, D. M., Edwards, R., Agarwal, R., Bakris, G., Bull, S., Cannon, C. P., Capuano, G., Chu, P. L., de Zeeuw, D., Greene, T., Levin, A., Pollock, C., Wheeler, D. C., Yavin, Y., Zhang, H., … CREDENCE Trial Investigators (2019). Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. The New England journal of medicine, 380(24), 2295–2306. https://doi.org/10.1056/NEJMoa1811744
4. Heerspink, H. J. L., Stefánsson, B. V., Correa-Rotter, R., Chertow, G. M., Greene, T., Hou, F. F., Mann, J. F. E., McMurray, J. J. V., Lindberg, M., Rossing, P., Sjöström, C. D., Toto, R. D., Langkilde, A. M., Wheeler, D. C., & DAPA-CKD Trial Committees and Investigators (2020). Dapagliflozin in Patients with Chronic Kidney Disease. The New England journal of medicine, 383(15), 1436–1446. https://doi.org/10.1056/NEJMoa2024816