

**Dapagliflozin, advanced chronic kidney disease and mortality:
new insights from the DAPA-CKD trial**

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In the general population both, decreasing estimated glomerular filtration rate (eGFR) and increasing albuminuria are well-established predictors of overall mortality. The presence of diabetes mellitus further potentiates this relationship ¹. In chronic kidney disease (CKD) stages 4-5 about 50% of the patients suffer from cardiovascular disease, and cardiovascular mortality accounts for ~40-50% of all deaths in patients with CKD stage 4 as well as patients with end-stage kidney disease (ESKD), compared with 26% in controls with normal kidney function ². In terms of cardiovascular disease and mortality, the relative importance of heart failure, valvular and sudden cardiac death, but not ischemic heart disease, increases as CKD progresses ². In a multitude of studies in subjects with advanced CKD, correction for classical cardiovascular risk factors, such as hypertension, diabetes mellitus and dyslipidaemia, did not neutralise the impact of CKD on cardiovascular risk ³ supporting the conclusions of a large meta-analysis that diabetes and kidney disease serve as independent predictors of clinical outcomes ¹. These observations underline the importance of non-traditional, CKD-specific cardiovascular risk factors and may explain at least in part why traditional strategies to improve cardiovascular outcome have largely failed in the context of CKD ⁴. Also, this emphasizes the need to not only identify pathological mechanisms adversely affecting the cardiovascular system in CKD but to develop novel therapeutic strategies. However, in most outcome trials conducted in the different fields of cardiology, patients with advanced CKD have been excluded resulting in an unfortunate and serious lack of evidence-based recommendations for this particular high-risk group.

In this issue of the European Heart Journal, Heerspink et al.⁵ present a prespecified analysis from the randomized, placebo-controlled DAPA-CKD (Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease) trial ⁶, in which they studied the effects of the SGLT2 inhibitor dapagliflozin on morbidity and mortality in patients with CKD. The trial had been performed in a population of diabetic but also non-diabetic CKD patients with a mean eGFR of 43 ml/min/1.73m². In DAPA-CKD, dapagliflozin as compared to placebo led to a significant reduction in the primary composite endpoint of sustained $\geq 50\%$ eGFR decline, ESKD, renal or cardiovascular death as well as hospitalisation for heart failure. In the present analysis, the

authors now show that among the 247 deaths in DAPA-CKD (i.e., 5.7 % of the overall population) 37% were due to cardiovascular causes, 41% due to non-cardiovascular causes, and 22% were of undetermined cause. Over a median follow-up of 2.4 years, dapagliflozin led to a highly significant 31 % risk reduction of all-cause mortality with a significant reduction in both, patients with and without diabetes; moreover, the results were consistent across all other pre-specified subgroups. Interestingly, the effect on all-cause mortality was largely driven by a significant 46 % relative risk reduction of non-cardiovascular death while the effect on cardiovascular death was not significant. Albeit only seen in a small number of patients and only described as a post-hoc analysis, the reduction in non-cardiovascular deaths by dapagliflozin was mainly driven by a reduction in deaths due to infections and malignancies.

The authors should be congratulated for conducting this landmark trial in the under-investigated population of high risk patients with advanced CKD and for providing these prespecified analyses to the scientific community. The results of this mortality analysis are important for several reasons. First, our current knowledge on the causes of death in patients with CKD is mainly based on observational studies with the inherent limitations of medical databases and registers such as lack of adjudication and potential misclassification. In the DAPA-CKD trial, mortality data were adjudicated by an independent events committee and they are derived from a very well characterized study population. The DAPA-CKD data thus extend our knowledge on the causes of death in patients with advanced CKD in that non-cardiovascular deaths occurred at a similar frequency as cardiovascular deaths (see above). Among the non-cardiovascular deaths, patients mainly died because of infection (19%) and malignancies (11%) while cardiovascular deaths mostly resulted from sudden cardiac death (21%) followed by 5.5% due to heart failure and only in 4.5% of the cases from acute MI. This is remarkably similar to observations in diabetic patients on dialysis, for example in the 4D trial⁷, where sudden cardiac death was the most prominent cause of cardiovascular mortality. The important insight from DAPA-CKD is thus, that in CKD the shift towards more and more sudden cardiac deaths occurs long before ESKD stage has been reached.

Interestingly, in the subgroup of patients without diabetes, non-cardiovascular death occurred more often than cardiovascular death (54% versus 30%), a result not observed in subjects with diabetes (non-cardiovascular death 38% versus cardiovascular death 39%), underscoring epidemiological data that diabetes is an additional cardiovascular risk promoter in CKD patients¹. DAPA-CKD enrolled 2/3 of all patients with diabetes and one third without a diagnosis of type 2 diabetes, but dapagliflozin led to a significant reduction in all-cause mortality in both subgroups. The second important message is therefore that in DAPA-CKD SGLT2 inhibitors treatment, a therapy originally developed to treat patients with type 2 diabetes, was life-saving in all CKD patients - irrespective of their diabetes status.

In a very large cohort study on non-cardiovascular mortality in advancing CKD, the relative importance of malignancy diminished, whereas infectious and diabetic complications increasingly contributed to deaths². While these Canadian data mostly have been reproduced in subsequent studies, it is important to note that such studies are all based on ICD-9 or -10 codes and causes of death have hardly ever been adjudicated in an independent fashion. The more important are the adjudicated DAPA-CKD non-cardiovascular deaths (41 % of the overall mortality). The beneficial effect of dapagliflozin on deaths due to infections raises the hypothesis that SGLT2 inhibitors may exhibit modulatory effects on inflammatory processes and immune function beyond the cardiovascular system and the kidney.

A limitation of the present post-hoc analysis of the DAPA-CKD trial is that the findings are based on a relatively low number of events, in particular in non-diabetic patients, as 80% of the deaths clustered in the subgroup with diabetes. Thus, in particular in non-diabetic patients the effects of an SGLT2 inhibitor on infection- or cancer-related mortality can at best be hypothesis generating but deserve further evaluation in clinical studies and experimental approaches. While the authors propose potential mechanisms by which dapagliflozin or, more likely, SGLT2 inhibitors in general might contribute to such benefits, there is a significant likelihood for chance findings given the low event rates. And finally, as with all large clinical trials, a common limitation is that “healthier” patients tend to be included, which renders an extrapolation to all patients with advanced CKD difficult. Nevertheless, we eagerly await

subgroup analyses of particular, more homogenous DAPA-CKD patients, such as the 270 patients with IgA-nephropathy.

Taken together, the data from DAPA-CKD, in conjunction with the results from other recently published SGLT2 inhibitor trials in patients with heart failure and reduced ejection fraction, position the class of SGLT2 inhibitors far beyond their original use in patients with type 2 diabetes. For the cardiovascular high-risk population of patients with CKD, SGLT2 inhibition with dapagliflozin provides for the first time a treatment option to significantly improve the prognosis and to reduce mortality – independent of the presence of diabetes. Within the next few years, additional studies with SGLT2 inhibitors in CKD patients will report (e.g. EMPA-KIDNEY with empagliflozin), but now it is on us - nephrologists, cardiologists and all health care providers treating patients with CKD – to ensure that these life-saving therapies are implemented. For the treatment of patients with diabetes, a subset of members of the writing groups of the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD) consensus document 2020, and the European Society of Cardiology (ESC) guidelines 2019 have recently published a call for action to ensure that clinical inertia does no longer lead to the low prescription of evidence-based life-saving therapies in high risk patients ⁸. The data published by Heerspink et al. extend this call to patients with CKD: “*Apply the evidence originating from large studies and provide the best therapy possible in daily practice*”.

Legend

Figure: Effect of SGLT2 inhibitors in patients with CKD or HFrEF. * Data from DAPA-CKD^{5,6}; # data from a meta-analysis from DAPA-HF and EMPEROR-REDUCED⁹. CKD: Chronic kidney disease; HFrEF: Heart failure with reduced ejection fraction

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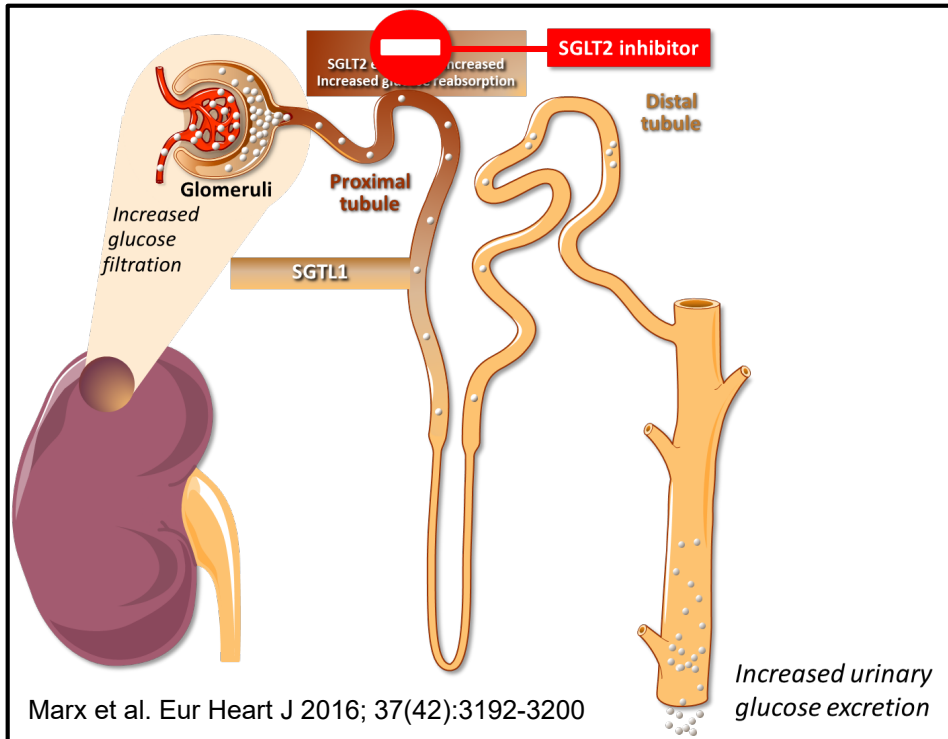
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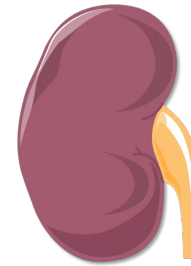
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Effect of SGLT2 inhibitors in patients with CKD or HFrEF

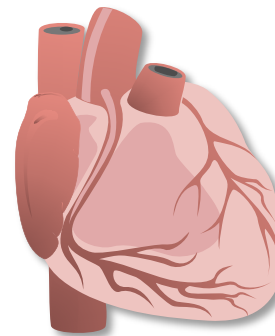


Patients with CKD*



- $\geq 50\%$ eGFR decline ↓
- ESKD ↓
- CV death or HF hospitalisation ↓
- Mortality ↓

Patients with HFrEF#



- Mortality ↓
- CV death ↓
- First HF hospitalisation ↓
- Kidney outcome composite ↓