The impact of frailty on the effects of empagliflozin: post-hoc analyses from the EMPA-KIDNEY trial

Dr Kaitlin Mayne
Nuffield Dept. of Population Health, University of Oxford
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Introduction

In EMPA-KIDNEY, the effects of empagliflozin on kidney disease progression were broadly consistent across patient subtypes by baseline diabetes status, eGFR, uACR and kidney disease aetiology. However, uncertainty appears to exist surrounding the risk-benefit profile of disease-modifying drugs (such as SGLT2 inhibitors) in older patients with frailty who have combinations of multiple disease characteristics.

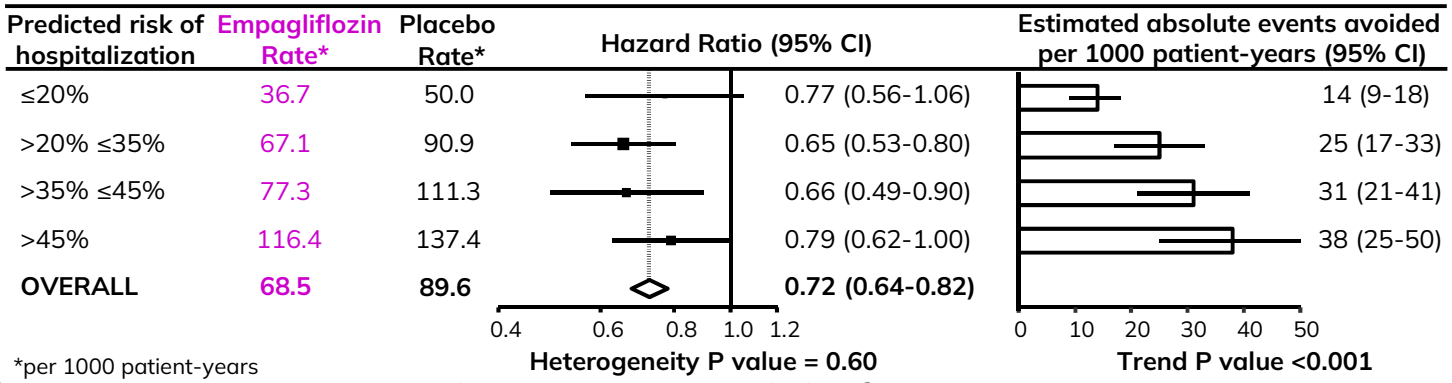
Methods

EMPA-KIDNEY included 6609 participants with CKD, detailed methods & primary results are reported elsewhere.[1] Baseline predicted risk of hospitalization during follow-up, derived from logistic regression models, was used as the primary frailty indicator. Subgroups were categorized by splitting predicted risk of hospitalization into approximate thirds with further dichotomization of the top third. Pre-specified outcomes were assessed in Cox regression models with interaction terms.

Results

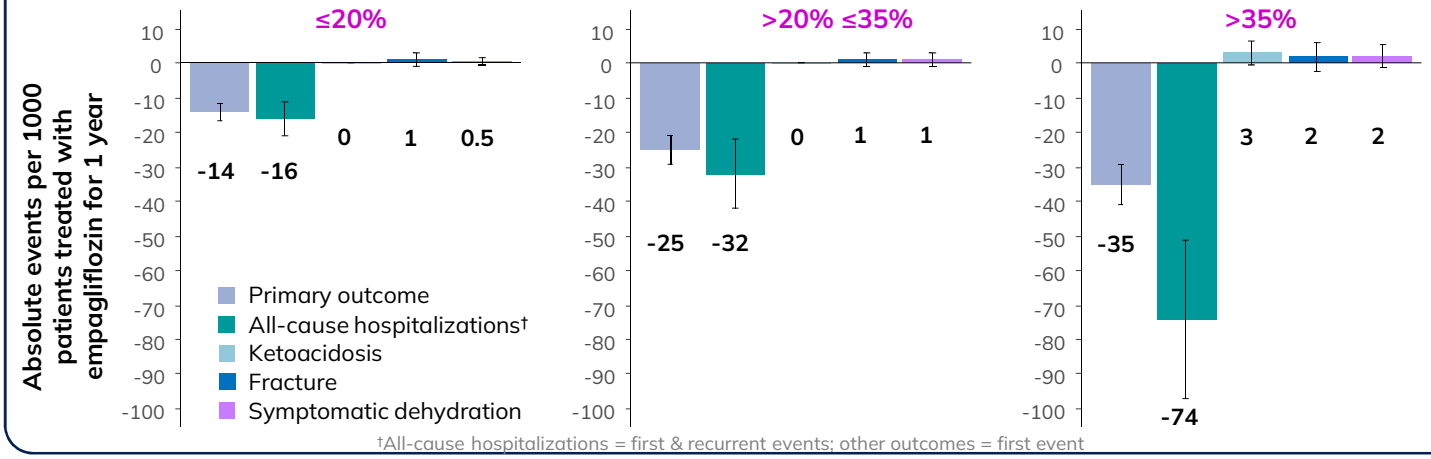
During 2 years' median follow-up, 1995 participants were hospitalized at least once (empagliflozin 960 vs placebo 1035; hazard ratio 0.86, 95% CI 0.78-0.95). The strongest predictors of hospitalization were NT-proBNP, poor mobility (EQ-5D) and diabetes. Median (Q1-Q3) predicted risk of hospitalization was 27% (18-40). The relative effects of empagliflozin were consistent irrespective of frailty but absolute benefits were greater in frailer participants (*Figure 1*); and benefits greatly exceeded potential harms (*Figure 2*).

Figure 1: Effects of empagliflozin on the primary outcome (progression of kidney disease* or cardiovascular death) by predicted risk of hospitalization



*Defined as initiation of dialysis/transplant, sustained eGFR<10 mL/min/1.73m^2, ≥40% sustained eGFR decline or renal death

Figure 2: Absolute benefits & harms of empagliflozin per 1000 patient-years by predicted risk of hospitalization



†All-cause hospitalizations = first & recurrent events; other outcomes = first event

Conclusions

The relative effects of empagliflozin were consistent irrespective of frailty (based on predicted risk of hospitalization). Larger absolute risk reductions were observed in patients with the highest level of frailty. Empagliflozin was safe and well-tolerated across frailty categories in EMPA-KIDNEY. These results support the use of SGLT2 inhibitors in CKD according to clinical guidelines, irrespective of frailty.

Reference: 1. The EMPA-KIDNEY Collaborative Group. N Engl J Med. 2023;388(2):117-127. CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; uACR = urinary albumin-to-creatinine ratio; SGLT2 = sodium–glucose cotransporter 2; NT-proBNP = N-terminal pro B-type natriuretic peptide. The EMPA-KIDNEY trial was initiated by the University of Oxford who led its design, analysis, & reporting with a Steering Committee of expert collaborators; and funded & sponsored by Boehringer Ingelheim with financial support from Eli Lilly & the UK Medical Research Council (MRC).