Diabetes UK Professional Conference, Manchester (Oral)

Are the cardiovascular risk reductions seen with empagliflozin in the EMPA-REG OUTCOME trial explained by conventional cardiovascular risk factors?

RL Coleman[1], A Gray[2], UC Broedl[3], D Fitchett[4], JT George[5], HJ Woerle[3], B Zinman[6,7] and RR Holman[1]

Diabetic Medicine (2017);34 (Suppl 1):5 - 35. doi:10.1111/dme.9_13303

[1]Diabetes Trials Unit, University of Oxford, Oxford, UK, [2]Health Economics Research Centre, University of Oxford, Oxford, UK, [3]Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany, [4]St Michael's Hospital, Division of Cardiology, University of Toronto, Toronto, Canada, [5]Boehringer Ingelheim Ltd, Bracknell, UK, [6]Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Canada, [7]Division of Endocrinology, University of Toronto, Toronto, Canada

Aims: To estimate the degree to which cardiovascular risk reductions demonstrated with empagliflozin administration in the EMPA-REG OUTCOME trial might be explained by changes observed in conventional cardiovascular factors during the study.

Methods: UKPDS Outcomes Model v2 was used to simulate three year cardiovascular event rates utilising annual patient-level data from 7,020 EMPA-REG OUTCOME participants that included atrial fibrillation, smoking, albuminuria, HDL-cholesterol, LDL-cholesterol, systolic blood pressure, HbA1c, heart rate, white cell count, haemoglobin and estimated glomerular filtration rate, as well as history of ischaemic heart disease, heart failure, amputation, blindness, renal failure, stroke, myocardial infarction or ulcer. Multiple simulations were performed for each participant to minimise first and second order uncertainty and to optimise the precision of the confidence intervals surrounding the cardiovascular risk point estimates. Estimated absolute event rates for empagliflozin and placebo assigned participants were used to calculate modelled cardiovascular relative risk reductions (RRRs).

Results: Compared to the observed RRRs, our simulated results suggest that empagliflozin would reduce absolute placebo rates for cardiovascular death by 3% (˜8% of 37% RRR observed), fatal and nonfatal myocardial infarction by 2% (˜15% of 13% RRR observed), all-cause mortality by 4% (˜13% of 32% RRR observed) and fatal and nonfatal stroke by 6% (rather than the 18% relative risk increase observed).

Conclusions: Empagliflozin-associated changes in conventional cardiovascular risk factor values recorded in the EMPA-REG OUTCOME trial appear to explain only a small proportion of the actual cardiovascular risk reductions observed for key endpoints. Accordingly, alternative risk-reduction mechanisms need to be explored.