SAT-305

EFFECTS OF EMPAGLIFLOZIN VS PLACEBO ON CARDIORENAL OUTCOMES IN PEOPLE WITH TYPE 2 DIABETES AND PROTEINURIC DIABETIC KIDNEY DISEASE: INSIGHTS FROM EMPA-REG OUTCOME

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Methods: In total, 7020 people with type 2 diabetes and prior cardiovascular (CV) disease were randomised 1:1 to empagliflozin 25 mg, 10 mg, or placebo, and followed for a median of 3.1 years. Post-hoc, Cox regression was used to assess the effects of empagliflozin versus placebo on a cardiorenal composite outcome of end-stage kidney disease (ESKD), initiation of maintenance renal replacement therapy or sustained estimated glomerular filtration rate (eGFR) <15 ml/min/1.73 m²), sustained doubling of creatinine, or renal/CV death. Analyses were performed in participants with EMPA-REG OUTCOME-like criteria for ESKD and initiation of renal replacement therapy or sustained eGFR <30 ml/min/1.73 m² and UACR >1000 mg/g) versus a non-ECPR subgroup (eGFR ≥30 ml/min/1.73 m² or UACR ≤300 mg/g). Similarly, we analysed other secondary outcomes: a composite renal outcome; hospitalisation for heart failure (HHF) and CV death; and CV death. Safety outcomes of particular interest were acute renal failure (ARF) and hyperkalaemia (based on AE reporting).

Results: Among all 7020 participants, the post-hoc cardiorenal outcome occurred in 201/4648 [4.3%] of participants allocated to empagliflozin and 169/2325 [7.3%] allocated to placebo, a 43% reduction in relative risk [hazard ratio [HR] 0.57 [95% CI 0.46-0.70]).

Of the 7020 EMPA-REG OUTCOME participants, 643 (9.2%) met EMPA-REG OUTCOME-like criteria for proteinuric DKD. Empagliflozin versus placebo showed consistent treatment effects with an HR of 0.46 [95% CI 0.31-0.68] for the cardiorenal outcome [49/420 [11.7%] versus 48/221 [21.7%]). Similarly, consistent effects were observed for the renal composite outcome, CV death, and the composite of CV death and HHF (figure). Similar to the overall population, there was no increased risk with empagliflozin versus placebo in events consistent with ARF (53/422 [12.6%] versus 37/221 [16.7%]) or hyperkalaemia (13/422 [3.6%] versus 16/221 [7.2%]).

Moreover, the treatment effect of empagliflozin in both subgroups was consistent with the overall population (all interaction p-values >0.05).

Figure: Cardiorenal outcomes in people with proteinuric DKD versus others

Conclusions: In this exploratory analysis, beneficial effects of empagliflozin on cardiorenal outcomes including kidney disease progression were consistent in a CREDENCE-like post-hoc subgroup when using a cardiorenal outcome definition following the CREDENCE trial.

The EMPA-KIDNEY study will investigate effects of empagliflozin in a broader CKD population for a primary cardiorenal composite outcome, including patients with/without diabetes and notably also those with lower proteinuria levels.

MON-338

MODULATION OF GSK-3β EXPRESSION BY AMPK AMELIORATES DIABETIC KIDNEY INJURY BY PROMOTING IR PHOSPHORYLATION CASCADE

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Introduction: Insulin resistance is a systemic disorder that affects many organs and insulin-regulated pathways. Insulin signaling to the glomerular podocyte is important for normal kidney function and is implicated in the pathogenesis of diabetic nephropathy (DN). It has recently been found that GSK-3β may play a role in the pathogenesis of diabetes and DN; however, the specific mechanism is still unknown. We aimed to investigate whether GSK-3β has a role in the amelioration of podocyte injury and insulin resistance, thus suppressing the progression of DN. Moreover, the molecular mechanisms responsible for the effects were examined.

Methods: Podocyte insulin responses were investigated with western blotting, cellular glucose uptake assays and fluorescent imaging of the insulin receptor signalling. Quantitative (q)RT-PCR was employed to investigate changes in mRNA. Cell viability and motility were detected by CCK-8 and wound healing assay. 12-week-old healthy male db/db mice, with a mean body weight of 36.63±1.29 (mean±SD), were treated with either normal saline (n=6) or 500mg/kg AMPK agonist AICAR (n=6), or 35mg/kg GSK3β inhibitor AZD1080 (n=6) by subcutaneous injection at a daily dose for 8 days.

Results: Our results demonstrated that AMPK modulates podocyte IR level and enhances insulin-stimulated phosphorylation of PI3K/Akt cascades in high-glucose condition and diabetic db/db mice. Plus, AMPK prevented hyperglycemia-induced increase of GSK3β phosphorylation, ameliorated glucose uptake into podocytes, and improved podocyte viability and motility. Moreover, treatments for modulation of key proteins in AMPK-PI3K/Akt -GSK3β signaling results in a reduction of proteinuria and significant improvement in renal function and pathological damage in db/db mice (Fig 1).

Conclusions: All these results suggested that the pharmacologic activation of AMPK and inhibition of GSK3β might suppress the progression of DN and podocyte injury, rescue podocyte insulin resistance. AMPK-GSK3β pathway may be exploited as a therapeutic target for protection against podocyte injury and insulin resistance in DN.