Mediators of the benefit of sotaglitazarin in patients with worsening heart failure in SOLOIST-WHF

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Background: In SOLOIST-WHF, the dual SGLT1 and SGLT2 inhibitor sotaglitazarin (SOTA) reduced primary endpoint events – total occurrences of cardiovascular (CV) death and hospitalizations and urgent visits for heart failure (HF) – by 33% relative to placebo (PBO) among 1222 patients hospitalized for worsening HF. The extent to which treatment group differences in biomarkers assessed during study follow-up contributed to this benefit of SOTA is unknown.

Purpose: The contributions of 20 biomarkers (identified in published mediation analyses of SGLT2 inhibitors: HbA1c; weight; BMI; systolic and diastolic BP; heart rate; serum creatinine, urate, albumin, sodium, and magnesium; eGFR; hematocrit; hemoglobin; erythrocytes; total cholesterol; LDL-C; HDL-C; non-HDL-C; triglycerides) to the reduction of primary endpoint events by SOTA relative to PBO were quantified via mediation analyses to describe the mechanisms of SOTA.

Methods: Patients were randomized 1:1 to SOTA 200 mg/day (with possible increase to 400 mg/day) or PBO and followed for a median 9 months. Two conditions must be met for a biomarker to be a mediator: there had to be a treatment group difference on the biomarker and an association between the biomarker and risk of primary endpoint events. For the first condition, treatment group differences in change from baseline in each biomarker were analyzed by mixed effects repeated measures models. For the second condition, time-varying values of each biomarker were related to the risk of primary endpoint events by calculating the time-weighted moving average (TWMA) for each variable, using all values for a given patient. Each was analyzed in a competing risks marginal model for total events (stratified according to left ventricular ejection fraction at baseline and geographic region of enrollment), in which non-CV deaths were treated as competing terminal events and TWMA values were included as a time-varying covariate. The individual and joint mediation of those biomarkers determined to be mediators were assessed in competing risks marginal models that included treatment assignment. If biomarkers that would otherwise be included in multivariable models were strongly correlated (baseline values R² > 0.5), the marker with the greatest univariate mediation was included. All analyses were intention-to-treat.

Results: Among the biomarkers considered, serum urate, hemoglobin, and total cholesterol met the criteria for being mediators. Serum urate was the strongest single mediator, while the joint mediation for these three biomarkers was 22.3% (Figure 1).

Conclusion: In SOLOIST-WHF, a fraction of the benefit of SOTA was attributable to effects on biomarkers accounting for most of the treatment benefits of other SGLT2 inhibitors on CV death and HF events. Further investigation is therefore needed to identify what unique biomarker treatment effects might account for the majority of SOTA benefit.