Serum uric acid, influence of sacubitril/valsartan, and cardiovascular outcomes in heart failure with preserved ejection fraction: PARAGON-HF

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Background: Serum uric acid (SUA) is a biomarker of several pathobiologies relevant to the pathogenesis of heart failure with preserved ejection fraction (HFpEF), though by itself may also worsen outcomes. In HF with reduced EF, SUA is independently associated with adverse outcomes and sacubitril/valsartan reduces SUA compared to enalapril. These effects in HFpEF have not been delineated.

Purpose: To determine the prognostic value of SUA, relationship of change in SUA to quality of life and outcomes, and influence of sacubitril/valsartan on SUA in HFpEF.

Methods: We analyzed 4,795 participants from the Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF) trial. We related baseline hyperuricemia to the primary outcome (CV death and total HF hospitalization), its components, myocardial infarction or stroke, and a renal composite outcome. At the 4-month visit, the relationship between SUA change and Kansas City Cardiomyopathy Questionnaire overall summary score (KCCQ-OSS) and several biomarkers including N-terminal pro-B-type natriuretic peptide (NT-proBNP) were also assessed. We simultaneously adjusted for baseline and time-updated SUA to determine whether lowering SUA was associated with clinical benefit.

Results: Average age was 73±8 years and 52% were women. After multivariable adjustment, hyperuricemia was associated with increased risk for most outcomes (primary outcome HR 1.61, 95% CI 1.37, 1.90, Fig 1A). The treatment effect of sacubitril/valsartan for the primary outcome was not modified by baseline SUA (interaction p=0.11). Sacubitril/valsartan reduced SUA –0.38 mg/dL (95% CI: –0.45, –0.31) compared with valsartan (Fig 1B), with greater effect in those with baseline hyperuricemia (–0.50 mg/dL) (interaction p=0.013). Change in SUA was independently and inversely associated with change in KCCQ-OSS (p=0.019) and eGFR (p<0.001), but not NT-proBNP (p=0.52). Time-updated SUA was a stronger predictor of adverse outcomes over baseline SUA.

Conclusions: SUA independently predicts adverse outcomes in HFpEF. Sacubitril/valsartan significantly reduces SUA compared to valsartan, an effect that was stronger in those with higher baseline SUA, and reducing SUA was associated with improved outcomes.