Title: Lowering Uric acid in Normo-uricemic Hypertensive Patients has an Adverse effect on LV Mass Regression: Mechanistic Clinical Evidence for the Urate Paradox

Author: Christopher R. Gingles, Ruth Symon, Stephen J. Gandy, Allan D. Struthers, Graeme Houston, Thomas M MacDonald, Chim C. Lang, Peter T. Donnan, Jacob George

Abstract

BACKGROUND: Uric acid is the most abundant aqueous antioxidant in humans but becomes pro-oxidant under certain conditions. This urate paradox remains hitherto unproven in clinical studies. Left ventricular Hypertrophy (LVH) is a strong predictor of cardiovascular events and all-cause mortality. LVH regression occurs with good blood pressure control.

OBJECTIVES: We aimed to investigate the impact of lowering uric acid on LV mass (LVM) regression in a normo-uricemic cohort with well controlled hypertension, low oxidative stress and inflammation but residual LVH compared to previously reported cohorts with established disease.

METHODS: A randomised double-blind, placebo controlled, parallel group study was conducted in 62 patients with controlled hypertension and LVH, comparing 600mg/day allopurinol or placebo therapy for 12 months. The primary outcome was change in LVM as assessed by cardiac MRI. Secondary outcomes were changes in biomarkers of oxidative stress, endothelial function assessed by flow-mediated dilatation (FMD) and arterial stiffness.

RESULTS: Despite good blood pressure control, LVH regression was significantly reduced in the allopurinol cohort compared to placebo (Indexed LVM -0.18 ± 2.39 $g/m^{1.7}$ vs -1.60 ± 1.60 $g/m^{1.7}$; p=0.009). Oxidative stress markers (TBARs) were significantly higher in the allopurinol group vs placebo (0.26 ± 0.85uM vs -0.34 ± 0.83uM; p=0.007). Other markers of vascular function were not significantly different between the two groups.

CONCLUSIONS: In normo-uricemic well-controlled hypertensives with LVH, lowering uric acid further results in attenuated LV mass regression and increased oxidative stress by adversely impacting the redox balance, particularly in females.

Keywords: Allopurinol, uric acid, left ventricular hypertrophy, hypertension.