Nitrate’s Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction (NEAT-HFpEF)

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BACKGROUND: Exercise intolerance is a cardinal feature of heart failure (HF) with preserved ejection fraction (HFpEF) and perpetuates sedentary behavior, deconditioning and frailty. While nitrates are commonly prescribed for symptom relief in HFpEF, no study has tested their effect in HFpEF.

HYPOTHESIS: Isosorbide mononitrate (ISMN) will enhance activity tolerance in HFpEF and thus, daily activity as assessed by patient worn accelerometry devices (AXM).

METHODS: NEAT-HFpEF was a multi-center, randomized, double-blind, 12 wk crossover study of ambulatory HFpEF patients (n=110). Entry criteria included HF symptoms, EF ≥ 50% and objective clinical (HF hospitalization), biomarker (NT-proBNP) or echocardiographic evidence of HF. During each 6 wk phase of the crossover study, patients took no study drug for 2 weeks (Baseline/Washout), then 30 mg for one wk, 60 mg for one wk and 120 mg for two wks. The primary endpoint was average daily accelerometry units (ADAU) during 2 wks of 120 mg/day of ISMN versus placebo as assessed by hip worn, tri-axial AXM worn throughout the study. Secondary endpoints included alternate activity indices (hours active/day at 120 mg dose and ADAU during all doses (30-120 mg)), six minute walk distance (6MWD), quality of life (QOL) scores, NT-proBNP and dose response. Treatment effect (TE) analysis adjusted for phase, sequence, baseline values and random effect of each patient.

RESULTS: Baseline characteristics (median or %): Age (69 yrs), Female (57%), BMI (34.7 kg/m2), NYHA II (53%) or III (45%) symptoms, KCCQ QOL score (54), 6MWD (312 m). ISMN tended to decrease ADAU at the 120 mg dose (TE -381, p=0.06) and significantly decreased hours active/day during 120 mg (TE -0.3 hours, p=0.02) and ADAU during all doses, (TE -439, p=0.02). ADAU decreased progressively and significantly as the ISMN (but not placebo) dose increased. ISMN had no effect on 6MWD, QOL scores or NT-proBNP. Numerically more patients had side effects during ISMN.

CONCLUSIONS: These findings do not support use of ISMN in HFpEF. Reduced activity during ISMN is of concern as decreased activity promotes frailty. Data on activity from patient worn devices provides unique, patient-centric information about the impact of HF therapies on patient’s lives.

Disclosure:
M.M. Redfield: None. K.J. Anstrom: Research Grant; Significant; NIH. J.A. Levine: Research Grant; Modest; Boeing. Consultant/Advisory Board; Modest; Kersh Health Risk Management, Gentag, SP Health. B. Borlaug: Research Grant; Significant; Mast Therapeutics, Medtronic. Consultant/Advisory Board; Significant; Merck, Amgen, AstraZeneca. H. Chen: None. M.M. LeWinter: Research Grant;
Significant; NIH. **S.M. Joseph:** None. **S.J. Shah:** Research Grant; Significant; NIH, Actelion. Consultant/Advisory Board; Modest; AstraZeneca, Bayer, Alnylam. Consultant/Advisory Board; Significant; Novartis. **M.J. Semigran:** Other Research Support; Significant; St. Jude Medical. Consultant/Advisory Board; Significant; Broadview, Novartis. **G.M. Felker:** Research Grant; Significant; NIH, Roche Diagnostics, Novartis, Amgen, Otsuka, Singulex. Consultant/Advisory Board; Modest; Trevena, Merck, Celladon, Medtronic. Consultant/Advisory Board; Significant; Novartis, Amgen. **R.T. Cole:** None. **G. Reeves:** Employment; Significant; Thomas Jefferson University. Other Research Support; Significant; ResMed Foundation, Thoratec. **R.J. Tedford:** Other; Significant; Merck. **W. Tang:** Research Grant; Significant; National Institutes of Health. **S.E. McNulty:** None. **E.J. Velazquez:** None. **M.R. Shah:** None. **E. Braunwald:** None.