Abstract: P4473

**Brain renin-angiotensin system blockade with firibastat, an orally active, central acting aminopeptidase A inhibitor prodrug prevents cardiac dysfunction after myocardial infarction in mice**

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Introduction: Brain renin-angiotensin system (RAS) hyperactivity has been implicated in sympathetic hyperactivity and progressive left ventricular (LV) dysfunction after myocardial infarction (MI). Brain angiotensin III, generated by aminopeptidase A (APA), is one of the main effector peptides of the brain RAS in the control of cardiac function.

Purpose: We hypothesized that orally administered firibastat (previously named RB150), an orally central acting APA inhibitor prodrug, would attenuate heart failure (HF) development after MI in mice, by blocking brain RAS hyperactivity.

Methods: Two days after MI induced by the left anterior descending artery ligation, adult male CD1 mice were randomized to three groups, for four to eight weeks of oral treatment with vehicle (MI+vehicle), firibastat (150 mg/kg; MI+firibastat) or the angiotensin I converting enzyme inhibitor enalapril (1 mg/kg; MI+enalapril) as a positive control.

Results: From one to four weeks post-MI, brain APA hyperactivity occurred, contributing to brain RAS hyperactivity. Firibastat treatment during four weeks after MI normalized brain APA hyperactivity, with a return to the control values measured in the sham group. Four and six weeks after MI, MI+firibastat mice had a significant lower LV end-diastolic pressure, LV end-systolic diameter and volume, and a higher LV ejection fraction than MI+vehicle mice. Moreover, the mRNA levels of biomarkers of HF (Myh7, Bnp and Anf) were significantly lower following firibastat treatment. For a similar infarct size, the peri-infarct area of MI+firibastat mice displayed lower levels of mRNA for markers of fibrosis such Ctgf and collagen types I and III than MI+vehicle mice.

Conclusions: Chronic oral firibastat administration after MI in mice normalizes brain APA hyperactivity, thereby normalizing brain RAS hyperactivity, whilst preventing cardiac dysfunction and attenuating cardiac hypertrophy and fibrosis.