A Randomized, Placebo Controlled Trial of Late Na Channel Inhibition (ranolazine) in Coronary Microvascular Dysfunction (CMD): Impact on Angina and Myocardial Ischemia

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Background:
Patients with persistent symptoms and signs of myocardial ischemia and no obstructive coronary artery disease (CAD) often have coronary microvascular dysfunction (CMD), evidenced by limited coronary flow reserve (CFR) on invasive coronary testing and abnormal stress myocardial perfusion reserve on cardiac magnetic resonance imaging (CMRI). Because the mechanistic basis for this syndrome is unclear and outcome trials are lacking, there is no recognized standard of care for such patients. We tested the hypothesis that myocardial ischemia is a mechanistic pathway for angina in CMD using late-Na channel inhibition (ranolazine).

Methods:
We conducted a randomized, double-blinded, placebo-controlled, cross-over trial of oral ranolazine 500-1,000 mg twice daily for 2 weeks in women and men with symptoms and signs of myocardial ischemia, no obstructive CAD, and abnormal CFR or CMRI myocardial perfusion reserve index (MPRI). The outcomes are angina (Seattle Angina Questionnaire [SAQ]) and angina frequency measured by diary (primary), MPRI and diastolic function on CMRI (secondary), and SAQ score change is related to myocardial perfusion change. The Women's Ischemia Syndrome Evaluation (WISE) Coronary Angiography and CMRI core laboratories qualified and analyzed the measures.

Results:
Between March 22, 2011 and April 20, 2015, 435 subjects were screened, 136 (91% women) were enrolled, randomized, and are in follow-up. Baseline data show a mean age 54±12 yrs, 18% diabetes, 54% hypertension, 6% current smoking, body mass index (BMI) of 29±7. The final patient will complete follow-up and data analysis will be concluded by July 30, 2015. The following data will be presented: safety data, efficacy data, SAQ domains (subscale and summary scores), angina diaries, and CMRI variables (global, mid-ventricular and subendocardial MPRI, diastolic function).

Conclusions:
This trial is the first test of the hypothesis that myocardial ischemia is a mechanistic pathway for angina in CMD subjects in the absence of obstructive CAD using late-Na channel inhibition. The results will provide the needed information for design and implementation of a large, definitive outcome trial to improve the morbidity and mortality of patients with CMD.

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