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

Hiroaki Shimokawa, MD, PhD
Professor and Chairman
Department of Cardiovascular Medicine, Tohoku University, Sendai, Japan

No conflict of interest to disclose
Functional Anatomy of the Coronary Circulation

Epicardial (conduit) arteries

- Endothelium-dependent regulation

Pre-arterioles

- Myogenically sensitive regulation

Arterioles

- Metabolic regulation

(Camici PG, Crea F. NEJM. 2007;356:830-40.)

Arterioles

- Pre-arterioles

- Conduit arteries

- Endothelial cells

- Vascular smooth muscle cells

- Myocardial metabolic demand

- Autonomic nervous system

- Adventitia (vasa vasorum, adipose cells, etc.)

- Blood (coagulation, fibrinolysis)

Poor prognosis of patients with coronary microvascular dysfunction (CMD) (WISE Study)

Ranolazine Improves Angina in Women With Evidence of Myocardial Ischemia But No Obstructive Coronary Artery Disease

Puja K. Mehta, MD,* Pavel Goykhman, MD,* Louise E. J. Thomson, MBC;B;† Chrisandra Shufelt, MD, MS,* Janet Wei, MD,* YuChing Yang, PhD,* Edward Gill;† Margo Minissian, NP,* Leslee J. Shaw, PhD;‡ Piotr J. Slomka, PhD;‡ Melissa Slivka, MD,* Daniel S. Berman, MD;† C. Noel Bairey Merz, MD*

Los Angeles, California; and Atlanta, Georgia

OBJECTIVES We conducted a pilot study for a large definitive clinical trial evaluating the impact of ranolazine in women with angina, evidence of myocardial ischemia, and no obstructive coronary artery disease (CAD).

BACKGROUND Women with angina, evidence of myocardial ischemia, but no obstructive CAD frequently have microvascular coronary dysfunction. The impact of ranolazine in this patient group is unknown.

METHODS A pilot randomized, double-blind, placebo-controlled, crossover trial was conducted in 20 women with angina, no obstructive CAD, and ≥10% ischemic myocardium on adenosine stress cardiac magnetic resonance (CMR) imaging. Participants were assigned to ranolazine or placebo for 4 weeks separated by a 2-week washout. The Seattle Angina Questionnaire and CMR were evaluated after each treatment. Invasive coronary flow reserve (CFR) was available in patients who underwent clinically indicated coronary reactivity testing. CMR data analysis included the percentage of ischemic myocardium and quantitative myocardial perfusion reserve index (MPRI).

RESULTS The mean age of subjects was 57 ± 11 years. Compared with placebo, patients on ranolazine had significantly higher (better) Seattle Angina Questionnaire scores, including physical functioning (p = 0.046), angina stability (p = 0.008), and quality of life (p = 0.021). There was a trend toward a higher (better) CMR mid-ventricular MPRI (2.4 [2.0 minimum, 2.8 maximum] vs. 2.1 [1.7 minimum, 2.5 maximum], p = 0.074) on ranolazine. Among women with coronary reactivity testing (n = 13), those with CFR ≤3.0 had a significantly improved MPRI on ranolazine versus placebo compared to women with CFR >3.0 (Δ in MPRI 0.48 vs. −0.82, p = 0.04).

CONCLUSIONS In women with angina, evidence of ischemia, and no obstructive CAD, this pilot randomized, controlled trial revealed that ranolazine improves angina. Myocardial ischemia may also improve, particularly among women with low CFR. These data document approach feasibility and provide outcome variability estimates for planning a definitive large clinical trial to evaluate the role of ranolazine in women with microvascular coronary dysfunction. (Microvascular Coronary Disease In Women: Impact Of Ranolazine; NCT00570089). (Am Coll Cardiol Img 2011;4:514–22) © 2011 by the American College of Cardiology Foundation
Summary of the RWISE Study

Strengths
• Design: Randomized, placebo-controlled, double-blind study.
• Effects: Subjects with more severe CMD might benefit from ranolazine.
• Incidence of side effect was comparable between ranolazine and placebo.

Weaknesses
• Basically negative
• Indefinite inclusion criteria (CFR, CMRI)
• Short-term treatment (2 weeks)
• Female predominant (96%)
• Use of SAQ for women
Future Perspectives of CMD

- In the CMD patients with low CFR, ranolazine might be one of possible therapeutic options.
- Further trials with a large number of patients with low CFR will elucidate the effectiveness of ranolazine for CMD.

How to diagnosis CMD?
(Flow wire, MRI, PET, Echo, Lactate production, etc.)

Pathophysiology of CMD?
- Ranolazine (RWISE)
- CMD (Low CFR)
- CMD (Preserved CFR)

Other possible treatments
1. Classical anti-ischemic drugs
2. Other anti-ischemic drugs
3. Alternative forms of therapy