

**Residency Program**  
**Drug Information Response Documentation**

**Resident Name:** Noel Forrett, Pharm.D.      **Preceptor Name:** Walt Schroeder, Pharm.D.

**Name of Rotation:** Erie County Medical Center Medicine C (Cardiology/CCU)

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**Source Name & Title:** Joseph Zizzi Jr., M.D.

**Specific Question:** What is the safety and efficacy of ranolazine for the treatment of chronic angina?

**Type of Response (please underscore):**      Short Answer      Long Answer

**Type of Long Answer Response (please underscore):**  
**Pharmacy & Therapeutics Review / Drug Review / Newsletter / Complex Literature Evaluation**

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**Background:**

Ranolazine (Ranexa®) is a recently-introduced product indicated for the treatment of chronic angina in combination with amlodipine, beta-blockers or nitrates.<sup>1</sup> With a unique mechanism of action that improves diastolic function and myocardial oxygen demand secondary to altered myocardial sodium and calcium dynamics, ranolazine represents a novel therapeutic approach to the treatment of chronic angina.<sup>2-5</sup> As such, interest in this compound has been increasing recently, although most clinicians have limited familiarity with the clinical data supporting the use of ranolazine. Therefore, the objective of this report is to review the available data from recent pivotal clinical trials evaluating the efficacy and safety of ranolazine for the treatment of chronic angina.

**Literature Review:**

A report published in 2004 described the results of a randomized, double-blind, placebo-controlled investigation to evaluate the effect of ranolazine monotherapy on the primary efficacy endpoint of exercise duration at trough, as well as overall therapeutic safety.<sup>6</sup> A total of 191 patients at least 21 years old with documented coronary artery

disease and a minimum three-month history of exertional angina responding to therapy with beta-blockers, calcium channel blockers, and/or long-acting nitrates were enrolled. Of these patients, 175 subjects completed at least 3 of 4 one-week crossover periods during which they were randomized in to receive either placebo or ranolazine 500, 1000 or 1500 mg orally twice daily (for inclusion in the efficacy analysis, patients had to have completed at least  $\frac{3}{4}$  study periods). At the end of the one-week periods, subjects performed an exercise tolerance test 4 and 12 hours after dosing to approximate testing at peak and trough plasma levels, and had to abstain from sublingual nitroglycerin for at least 60 minutes prior to testing. During the four crossover periods, all prophylactic and anti-anginal medications were discontinued. For all ranolazine doses, duration of exercise at trough was significantly ( $p < 0.001$ ) improved versus placebo (500 mg BID = 23.8 seconds longer, 1000 mg BID = 33.7 sec, 1500 mg BID = 45.9 sec). Dose-dependent statistically significant ( $p < 0.0001$ ) improvements in secondary endpoints of time to angina and time to 1 mm ST-segment depression during exercise were also noted for all ranolazine doses versus placebo. Overall adverse event rates were similar for ranolazine 500 mg BID and placebo (16.0% vs 15.6% respectively), with dose-dependent increases in overall and specific adverse event rates. Adverse events occurring more frequently than placebo included dizziness (1.1-12.3%), nausea (<1 – 8.6%), asthenia (0 – 6.4%), constipation (0 – 4.3%), headache (<1 - 2.7%), and sweating (0 – 2.7%). No patients were released from or discontinued the study due to increases in QTc interval, a known side effect of ranolazine. Overall, the data demonstrates superiority of ranolazine versus placebo for increasing exercise tolerance in patients with chronic angina previously maintained on one or more anti-anginal medications. However, because the design of the trial included a discontinuation of the patients' medications except for rescue sublingual nitroglycerin, extrapolation to a general population of patients commonly taking one or more anti-anginal medications is difficult. Additionally, based on the 4-way crossover design, it is impossible to estimate without further data regarding the washout periods whether patients were subject to cumulative effects of ranolazine. Finally, the overall study periods of one-week per phase were relatively short, implying on one hand that a difference in primary endpoint data in such a short time frame may be of special significance, but failing on the other hand to generate any long-term efficacy and/or safety data.

A separate report also published in 2004 described the results of a double-blind, parallel-group study designed to evaluate the effect of ranolazine in combination with other therapeutic modalities on exercise tolerance in patients with chronic angina.<sup>7</sup> A total of 823 patients chronically taking antianginal therapy with either atenolol 50 mg daily, diltiazem 180 mg daily, or amlodipine 5 mg daily were enrolled and randomized to receive either placebo or oral ranolazine 750 mg or 1000 mg twice daily for 12 weeks. Groups were well-matched for prior medical history, gender and other characteristics, and background medications and doses remained unchanged throughout the study. Of the 823 enrolled patients, efficacy data from 791 subjects were included in final analysis, following attrition primarily due to dropout. The primary efficacy endpoint was exercise duration (exercise tolerance test) at trough plasma levels, approximately 12 hours following the last dose of study medication. Tests were performed at study weeks 2, 6 and 12. Subjects randomized to either dose of ranolazine exhibited a greater exercise tolerance than placebo at all measurement times ( $p < 0.001$ , week 2;  $p < 0.008$ , week 6;  $p < 0.02$ , week 12). Pooled data of both ranolazine groups demonstrated increased exercise tolerance at both trough and peak levels ( $p = 0.03$  &  $p < 0.02$  respectively). Analysis of a secondary endpoint of frequency of anginal attacks also demonstrated superiority of ranolazine (750 mg = 2.5 attacks/week,  $p = 0.006$ ; 1000 mg = 2.1 attacks/week,  $p < 0.001$ ) versus placebo (3.3 attacks/week). Study safety data demonstrated an increased incidence of adverse event reporting for the ranolazine groups (750 mg = 31.2%; 1000 mg = 32.7%) versus placebo (26.4%). The most frequently-reported dose-related adverse events included constipation, dizziness, nausea and asthenia ( $\leq 7.3\%$ , both ranolazine groups;  $\geq 0.7\%$ , placebo). Additionally, ranolazine groups exhibited significant increases in mean QTc interval versus placebo (750 mg = 6.1ms, 1000 mg = 9.2ms,  $p < 0.001$ ); no incidences of Torsades de Pointes were reported. Overall, the data appear to demonstrate clinical utility of adding ranolazine to existing therapy for patients maintained on anti-anginal therapies, with moderate risk of gastrointestinal and/or central nervous system adverse effects, and a potential risk of QTc interval prolongation. Unfortunately, no data was generated regarding ranolazine's efficacy at improving exercise tolerance or its clinical safety when used in combination with patients already maintained on maximal-dose antianginal therapies, a scenario likely to be encountered in clinical practice.

However, an additional report was recently published describing the results of an investigation designed to evaluate the efficacy of ranolazine added to maximum doses of amlodipine at controlling the frequency of anginal attacks in symptomatic patients with chronic angina.<sup>8</sup> Of 627 patients randomized in double-blind fashion to receive either placebo or ranolazine, 552 (274 ranolazine, 278 placebo) completed the study. Enrolled subjects included patients with documented history of cardiovascular events (significant CAD, prior MI, or positive stress echocardiogram) and minimum 3-month history of chronic stable angina who had been maintained on amlodipine 10 mg daily for at least two weeks prior to enrollment, who were still reporting  $\geq 3$  episodes of angina/week. Once enrolled, patients were maintained on amlodipine 10 mg daily and, for patients in the ranolazine arm, given a one-week run-in period of ranolazine 500 mg orally BID, then maintained on ranolazine 1000 mg orally BID for 6 weeks. Study populations for each treatment arm were well-matched for medical history, demographics and baseline characteristics. The primary efficacy endpoint was frequency of self-reported anginal attacks. The trimmed mean (eliminating significant outliers) of weekly anginal attacks demonstrated superiority of ranolazine versus placebo ( $2.88 \pm 0.19$  versus  $3.31 \pm 0.22$  attacks/week respectively;  $p=0.028$ ). Analysis of trimmed mean secondary endpoint data regarding weekly nitroglycerin consumption demonstrated similar superiority of ranolazine versus placebo ( $2.03 \pm 0.20$  versus  $2.68 \pm 0.22$  times/week respectively;  $p=0.014$ ). Safety data analysis demonstrated similar adverse event occurrence between groups (35.3% placebo, 39.9% ranolazine; no p-value reported), with primarily benign events reported. Adverse events occurring more frequently than placebo included constipation (8.9% vs 1.8%), peripheral edema (5.7% vs 2.8%), dizziness (3.9% vs 2.5%), nausea (2.8% vs 0.7%), and headache (2.8% vs 2.5%). Adverse event reporting was more frequent in women than in men. No comment was made regarding QTc interval differences between groups or whether any QTc interval changes were documented. Overall, the data support the use of ranolazine in patients with severe chronic angina refractory to maximal oral amlodipine therapy. Unfortunately, no additional “max-dose” antianginal therapies were investigated, which would be helpful in determining the role of ranolazine as an adjunct for patients refractory to other common therapies.

## **Summary:**

The available clinical data regarding ranolazine is relatively limited, primarily due to a small number of investigations having been conducted. At this time, ranolazine has been studied as monotherapy and as an element of combination therapy in association with moderate dose conventional modalities and maximal dose amlodipine. Based on the outcome analyses, amlodipine appears to be superior to placebo for increasing exercise tolerance, controlling anginal event frequency and reducing nitroglycerin use, however larger-scale, more extended-period studies may be warranted to clarify ranolazine's place in therapy – should the drug be added prior to or subsequent to maximizing existing therapies? It appears that in either case, a clinical benefit may be observed, but a potential cost: despite a limited percentage of relatively benign gastrointestinal and central nervous system side effects, both peripheral edema and QTc interval prolongation have been reported, each of which may significantly affect patient disposition, considering that much of the target treatment population may have limited capacity for tolerating these adverse events. At this time, based on potential cardiac disturbances, limited efficacy data, and an indication only as a component of combination therapy, it may be most prudent to maximize other antianginal therapies prior to initiating ranolazine.

#### **References:**

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