

# Ranolazine (Ranexa<sup>®</sup>) for Chronic Stable Angina

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## Summary

- ✓ **Ranolazine – an adjunctive treatment to beta-blockers, calcium channel blockers, or long-acting nitrates – is indicated for patients with chronic stable angina who have not responded to standard anti-anginal therapy.**
- ✓ **In three randomized controlled trials (RCTs), ranolazine, in combination with standard anti-anginal medications, led to modest but statistically significant improvements in exercise duration, and reductions in the frequency of angina episodes and nitroglycerin consumption, when compared to standard anti-anginal medications only. The clinical significance of these improvements is unknown. Most of the participants in studies were male and Caucasian. Thus, there are questions about the drug's efficacy in other populations.**
- ✓ **One RCT suggests that the addition of ranolazine to standard treatment is ineffective in reducing major cardiovascular events that are associated with acute coronary syndromes.**
- ✓ **The adverse effects reported with ranolazine include dizziness, nausea, asthenia (weakness), constipation, and headache. Long-term data from one trial indicate that there is no significant increase in the incidence of death or arrhythmia among those taking ranolazine.**
- ✓ **More clinical trials of ranolazine are needed to confirm its long-term safety, its optimal dosing, its efficacy in combination with full dose beta-blockers with or without calcium channel blockers, and its potential role in the treatment of other cardiovascular conditions.**

## The Technology

Ranolazine is a piperazine derivative that is indicated for the treatment of chronic stable angina.<sup>1</sup> The mechanism of action of ranolazine is unknown. One hypothesis is that it inhibits the late inward sodium channels.<sup>2</sup> The result is a reduction in intracellular calcium concentrations, which is

thought to improve diastolic function, decrease oxygen demand, and increase coronary blood supply.<sup>2</sup> Because ranolazine does not affect heart rate or blood pressure, it may be a useful alternative for patients who cannot tolerate or are unresponsive to current anti-anginal treatments. Because ranolazine may increase the risk of heart arrhythmias, it should only be used by patients whose symptoms are not controlled using long-acting nitrates, calcium channel blockers, or beta-blockers.<sup>1</sup> Ranolazine is not currently indicated for the treatment of unstable angina or for stable angina in patients who respond to treatment with conventional medications.

## Regulatory Status

Ranolazine (Ranexa<sup>®</sup>) is manufactured by CV Therapeutics Inc. (Palo Alto, CA).<sup>1</sup> It was approved by the US Food and Drug Administration (FDA) in January 2006.<sup>3</sup> Ranolazine is not currently licensed for sale in Canada.

## Patient Group

Angina pectoris is characterized by pain or pressure in the chest that may radiate to the left arm, neck, jaw, or face.<sup>4</sup> The symptoms may include dizziness, fatigue, and shortness of breath. Angina is usually caused by atherosclerotic coronary artery disease, when the coronary arteries that supply the heart with oxygen-rich blood become blocked with plaque deposits, resulting in myocardial ischemia (insufficient oxygen due to reduced blood flow).<sup>5</sup> Angina attacks can last several minutes and vary in frequency from occasional episodes to several episodes per day. The symptoms of stable angina are predictable and often occur with physical exertion or stress.

In Canada, cardiovascular disease is the leading cause of death among women and the second leading cause of death among men.<sup>6</sup> The 2000-2001 Canadian Community Health Survey estimated that 483,000 Canadians have angina.<sup>7</sup> The prevalence, which is similar among men and women, increases significantly after 50 years of age.<sup>6,7</sup> Coyle *et al.*<sup>8</sup> estimate that there are 47,000 new cases of angina in Canada each year. The average annual mortality due to chronic stable angina is 1% to 3%.<sup>9,10</sup> This relatively low mortality rate

is an important consideration when determining the merits of new drugs for symptom relief.

## Current Practice

Guidelines for the management of chronic stable angina have been released by the American College of Cardiology and the American Heart Association (ACC-AHA),<sup>5</sup> and the Canadian Cardiovascular Society (CCS).<sup>11</sup> The clinical management of stable angina involves relieving symptoms, slowing the progression of disease, and reducing the risk of myocardial infarction and premature death.<sup>4,5</sup> Beta-blockers, calcium channel blockers, and nitrates are used for symptomatic control. Most patients with moderate to severe angina need combination therapy with two or more drugs, which may lead to side effects that are associated with changes in blood pressure and heart rate.

In addition to lifestyle changes, medications that are used to reduce morbidity and mortality include acetylsalicylic acid (Aspirin), lipid-lowering therapy such as statins and fibrates, and angiotensin-converting enzyme (ACE) inhibitors. Some patients with chronic stable angina are unresponsive to combination drug therapy or experience undesirable side effects. These patients may benefit from an agent that does not affect heart rate or blood pressure. Patients with serious coronary artery disease may be candidates for revascularization procedures such as angioplasty or coronary artery bypass surgery.

## The Evidence

Three trials<sup>12-14</sup> have examined the role of extended-release ranolazine in chronic stable angina (Table 1). The MARISA trial<sup>12</sup> was a dose-comparison study. Compared with placebo, treatment with ranolazine significantly improved total exercise duration, time to angina, and time to 1 mm ST-segment depression. The results were consistent in subgroup analyses for diabetes, gender, history of heart failure, and age. Although statistically significant, the improvements were small and the clinical significance is unclear.

The efficacy of adding ranolazine to other anti-anginal medications – all given at typical starting doses – was evaluated in the CARISA trial.<sup>13</sup> The baseline characteristics were similar for all study groups. After 12 weeks of therapy, both doses of ranolazine (750 mg or 1,000 mg twice daily) significantly increased exercise duration and time to angina compared with placebo. The time to 1 mm ST-segment depression was not significantly different from that of the placebo group at

trough ranolazine levels. Patients receiving ranolazine experienced an average of one less angina episode and use of nitroglycerin per week compared to those given placebo. There was no evidence of rebound worsening of exercise performance when therapy with ranolazine was discontinued after 12 weeks.<sup>15</sup> While subgroup analyses indicated that the treatment effect of ranolazine was similar for diabetic and non-diabetic patients, ranolazine seemed to significantly improve glycemic control in diabetic patients.<sup>16,17</sup> This finding needs to be validated in a larger, prospectively designed study.

The ERICA trial<sup>14</sup> was designed to evaluate the benefit of ranolazine when it was used in therapy with a maximal dose of the calcium channel blocker amlodipine. A more representative population with chronic angina included patients who were experiencing  $\geq 3$  angina attacks weekly, despite therapy with amlodipine, and a higher proportion of patients with hypertension, previous myocardial infarction, and heart failure. The baseline characteristics were similar for all study groups. Unlike the MARISA and CARISA trials, the ERICA trial assessed physical activity level beyond treadmill testing. After seven weeks, the average number of angina episodes and nitroglycerin use per week were significantly lower for the group treated with ranolazine compared with placebo. These differences were small, with an average of 1.6 less angina episodes and 2.8 less uses of nitroglycerin per month, compared to those given placebo. The results were consistent with those of subgroup analyses for gender, age, and additional therapy using long-acting nitrates. Seattle Angina Questionnaire (SAQ) angina frequency scores were significantly improved in the ranolazine group versus placebo, but there were no differences for the other components. Patients with more frequent angina at baseline ( $>4.5$  episodes per week) seemed to have more pronounced improvement of symptoms.

No available trials have assessed the benefit of extended-release ranolazine when added to full-dose beta-blockers alone or in combination with calcium channel blockers. A randomized, double-blind, crossover trial<sup>18</sup> compared the effect of immediate-release ranolazine (400 mg three times daily) with that of atenolol (100 mg daily) or placebo in 158 patients. The results for exercise duration (treadmill or bicycle), time to angina onset, and 1 mm ST-segment depression were all significantly increased for atenolol and ranolazine when compared with placebo. The total exercise duration was significantly longer among those treated with ranolazine versus atenolol. The differences between ranolazine and atenolol were not statistically significant for time to angina onset and time to 1 mm

**Table 1: Clinical Trials of Extended-release Ranolazine in Chronic Stable Angina**

	<b>MARISA<sup>12</sup></b>	<b>CARISA<sup>13</sup></b>	<b>ERICA<sup>14</sup></b>
<b>Design</b>	randomized, double-blind, placebo-controlled, crossover; 4 weeks (n=191)	randomized, double-blind, placebo-controlled, parallel-group; 12 weeks (n=823)	randomized, double-blind, placebo-controlled, parallel-group; 7 weeks (n=565)
<b>Inclusion criteria</b>	age ≥21 years, chronic stable angina ≥3 months relieved by anti-anginal therapy	age ≥21 years, chronic stable angina ≥3 months relieved by anti-anginal therapy	≥18 years, chronic stable angina ≥3 months and ≥3 episodes of angina per week despite treatment with amlodipine 10 mg daily
<b>Participants' characteristics</b>	mean age 64.3 years; male 73.3%; Caucasian 91.1%; prior medical history: MI 52.3%, CHF classes I and II 16.8%, hypertension 64.4%, diabetes 24.1%, coronary angioplasty 32.5%, coronary artery bypass surgery 27.7%	mean age 63.9 years; male 77.5%; Caucasian 98.0%; prior medical history: MI 57.6%, CHF classes I and II 28.7%, hypertension 64.0%, diabetes 22.9%, coronary angioplasty 18.5%, coronary artery bypass surgery 17.6%	mean age 61.6 years; male 72.5%; Caucasian 98.5%; prior medical history: MI 79.8%, CHF classes I to III 51.5%, hypertension 89.0%, diabetes 19.0%, coronary angioplasty 10.4%, coronary artery bypass surgery 11.0%
<b>Treatment</b>	ranolazine 500 mg or 1,000 mg or 1,500 mg twice daily, or placebo; all other anti-anginals discontinued except sublingual nitroglycerin as needed	ranolazine 750 mg or 1,000 mg twice daily or placebo, in combination with 1 of diltiazem 180 mg, atenolol 50 mg, amlodipine 5 mg daily; sublingual nitroglycerin as needed	ranolazine 500 mg twice daily or placebo (1 week); ranolazine 1,000 mg twice daily or placebo (6 weeks); in combination with amlodipine 10 mg daily and long-acting nitrates or isosorbide mononitrate, if needed; sublingual nitroglycerin as needed
<b>Primary outcomes</b>	exercise duration on treadmill	exercise duration on treadmill	average weekly frequency of angina attacks
<b>Secondary outcomes</b>	time to angina onset and to 1 mm ST-segment depression	time to angina onset and to 1 mm ST-segment depression; frequency of angina attacks; frequency of nitroglycerin use	average weekly nitroglycerin consumption scores; SAQ scores for angina frequency, physical limitations, anginal stability, disease perception, treatment satisfaction
<b>Results</b>	<b>Mean difference from placebo (in seconds)<sup>1</sup>:</b> <b>Exercise duration:</b> 24 (p=0.003); 34 (p<0.001); 46 (p<0.001); placebo=506 <b>Time to angina(s):</b> 27 (p=0.005); 46 (p<0.001); 60 (p<0.001); placebo=407 <b>Time to 1 mm ST-segment depression(s):</b> 28 (p<0.001); 45 (p<0.001); 65 (p<0.001); placebo=443	<b>Mean difference from placebo (in seconds)<sup>2</sup>:</b> <b>Exercise duration:</b> 24 (p=0.03); 24 (p=0.03); placebo=510 <b>Time to angina(s):</b> 30 (p=0.01); 26 (p=0.03); placebo=441 <b>Time to 1 mm ST-segment depression(s):</b> 20 (p=0.10); 21 (p=0.09); placebo=424	<b>Mean angina attacks/week:</b> ranolazine 2.9, placebo 3.3 (p=0.028) <b>Mean nitroglycerin use/week:</b> ranolazine 2.0, placebo 2.7 (p=0.014)
<b>Study limitations</b>	crossover design presents difficulties for assessing optimal dosing; method of randomization and ITT analysis not reported; 88% of participants completed all 4 crossover periods; excluded patients with more severe heart failure (classes III and IV); study population 73.3% male and 91.1% Caucasian	ITT analysis not reported; compliance not assessed; excluded patients with more severe heart failure (classes III and IV); study population 77.5% male and 98% Caucasian	study population 72.5% male and 98.5% Caucasian

CHF=congestive heart failure; ITT=intention to treat, MI=myocardial infarction, SAQ=Seattle Angina Questionnaire; <sup>1</sup>results given for 500, 1,000, or 1,500 mg twice daily respectively, at trough levels; <sup>2</sup>results given for 750 mg or 1,000 mg twice daily respectively, at trough level.

ST-segment depression. The generalizability of these results is limited by small sample size, crossover study design, and outcomes reported at peak ranolazine levels that may overestimate the treatment effect at trough levels.

The study population in these trials was predominantly male. There is evidence from subgroup analyses that ranolazine may be less effective for symptom control among women,<sup>19</sup> but more trials that are powered to detect the difference are needed.

## Adverse Effects

In controlled trials, no serious adverse effects were attributed to ranolazine.<sup>1</sup> The most frequent adverse effects were dose-related and included dizziness, constipation, nausea, asthenia, and headache, all of which affected <10% of patients.<sup>1</sup> Subgroup evaluations in patients with reactive airway disease, congestive heart failure, and diabetes did not alter the frequency of adverse events observed in the broader patient population. Patients who were >75 years old experienced a higher rate of adverse events.<sup>1</sup> There is evidence that ranolazine prolongs the QT interval, which is a measure on an electrocardiograph (ECG) that may show a predisposition to heart arrhythmias. In these trials, no patient discontinued participation because of QT prolongation, and there were no reports of dangerous heart rhythms.<sup>1</sup> These studies were underpowered to detect rare side effects, and larger long-term trials are needed to confirm these results.

## Administration and Cost

Ranolazine is marketed in the US as an extended-release (ER) formulation available in 500 mg tablets. The recommended starting dose is 500 mg twice daily, which can be increased to a maximum of 1,000 mg twice daily as needed, in addition to standard anti-anginal medications.<sup>1</sup> Ranolazine is contraindicated in patients with hepatic impairment. Dosing adjustment recommendations for patients with renal impairment have not been established.<sup>1</sup>

There is no Canadian price for ranolazine, and the cost-effectiveness of using ranolazine as an adjunctive therapy is unknown. The current wholesale price for each 500 mg ER tablet is US\$2.83 (Celeste Marx, CV Therapeutics, Palo Alto CA: personal communication, 2007 March 7). Baseline and follow-up ECGs should be obtained to evaluate the effects of ranolazine on the QT interval.<sup>1</sup> Thus, therapy with ranolazine leads to additional costs for the drug and for follow-up tests.

## Concurrent Developments

Several pharmacological agents are being investigated for the treatment of angina.<sup>20,21</sup>

- An ongoing phase III trial is evaluating the ability of ivabradine, in combination with atenolol, to improve exercise tolerance among patients with stable angina.<sup>22</sup>
- Two inhibitors of fatty acid oxidation, trimetazidine and perhexiline, are available in other countries, but neither drug is approved in North America.<sup>21,23</sup>
- A phase II study is recruiting patients to examine the effect of fasudil (an inhibitor of rho kinase) on vascular function in patients with coronary artery disease.<sup>24</sup>
- An ongoing phase IV trial is evaluating the long-term safety and efficacy of testosterone for patients with chronic stable angina.<sup>25</sup>
- The use of gene therapy to promote blood-vessel growth is being investigated among patients with severe angina. Phase I and II clinical trials for VesCell™ (adult stem therapy using cells from the patient's blood) will soon start recruiting patients.<sup>26</sup>
- Enhanced external balloon counterpulsation, spinal cord stimulation, and transmyocardial laser revascularization are being investigated.<sup>23,27</sup>

## Rate of Technology Diffusion

Ranolazine is the first new drug used to treat angina in over 10 years. It may have potential as an adjunctive agent for patients who have not achieved an adequate response with other anti-anginal drugs in combination with beta-blockers, amlodipine, or nitrates.

MERLIN-TIMI 36 is a multi-national trial evaluating the impact of ranolazine on death and recurrent ischemic events among patients with acute coronary syndromes (ACS).<sup>28</sup> A total of 6,560 patients were randomized to receive ranolazine or placebo in addition to standard therapy. The median duration of treatment was 348 days. The results indicate that ranolazine did not produce a statistically significant reduction in time to first occurrence of any component of the primary endpoint composite of cardiovascular death, myocardial infarction, or recurrent ischemia [hazard ratio (HR): 0.92; 95% confidence interval (CI): 0.83 to 1.02; p=0.11]. Consistent with previous studies, ranolazine showed a statistically significant reduction in the incidence of recurrent ischemia alone (HR: 0.87; 95% CI: 0.76 to 0.99; p=0.03). The study also

evaluated the long-term safety of ranolazine. Patients receiving ranolazine had higher rates of QT prolongation requiring dose reduction compared with those receiving placebo (0.9% versus 0.3%). There was no statistical difference between the two groups in the primary safety endpoint of all-cause mortality and symptomatic documented arrhythmias during a median one-year follow-up. Although these findings suggest that ranolazine is ineffective in reducing major cardiovascular events among patients with ACS, positive results regarding long-term safety may support the use of ranolazine as an adjunctive agent for chronic stable angina.

## Implementation Issues

Because ranolazine should be used in combination with other anti-anginal drugs, the prescription of these drugs is not expected to change. Combination therapy with ranolazine is anticipated to add costs for the additional drug and follow-up ECGs. Ranolazine should not be prescribed for patients who are taking medications that increase the plasma levels of ranolazine or prolong the QT interval. More evidence is needed to clarify the clinical utility and safety of therapy with ranolazine.

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