



Department of Vermont Health Access

Therapeutic Class Review Miscellaneous Cardiac Drugs

Overview/Summary

Ranolazine is Food and Drug Administration approved for the treatment of chronic angina. It may be used in combination with amlodipine, β -adrenergic blocking agents (β -blockers), nitrates, calcium channel blockers (CCBs), anti-platelet therapy, lipid lowering therapy, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.¹⁻² It does not abate an acute angina episode, but rather is designed to minimize or prevent recurrent episodes from occurring. The mechanism of action of ranolazine is unknown. It is suggested that ranolazine inhibits the slow sodium channel in the cardiac muscle, thereby reducing sodium/calcium exchange and preventing the accumulation of calcium and diastolic stiffness.³ This in turn improves myocardial perfusion. Unlike other antianginal agents, ranolazine does not reduce heart rate or blood pressure. At maximal exercise, it does not increase the rate-pressure product, which is a measure of myocardial work.⁴

Angina occurs when the myocardial oxygen demand exceeds the oxygen supply, resulting in chest discomfort or pain. The currently available treatment options for chronic angina include nitrates, β -blockers and CCBs. These agents either decrease oxygen demand and/or increase oxygen supply.⁵ Nitrates, such as isosorbide dinitrate, isosorbide mononitrate, and transdermal nitroglycerin, reduce cardiac oxygen demand by decreasing left ventricular pressure and systemic vascular resistance and dilating coronary arteries. However, the use of nitrates as first-line agents has been limited because of tolerance that develops with chronic use. β -Blockers, such as atenolol and metoprolol, reduce heart rate and contractility by competitively blocking the response to β -adrenergic stimulation in the heart. β -blockers are recommended as first-line agents in patients with stable angina since they have been shown to reduce mortality following myocardial infarction.⁶ CCBs, such as amlodipine, diltiazem and verapamil, increase oxygen supply by producing coronary and peripheral vasodilatation, decreasing atrioventricular conduction and reducing contractility. CCBs also decrease cardiac oxygen demand by reducing systemic vascular resistance and arterial pressure.⁵ CCBs are often used because they are presumed to have similar efficacy and fewer side effects when compared to β -blockers. However, short-acting CCBs have been shown to increase the risk of cardiac events in patients with hypertension and nifedipine has been shown to increase mortality following acute ischemic syndromes.⁶ Differences in long-term rates of survival or myocardial infarction between classes of antianginal agents have not been studied.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Generic Availability
Ranolazine (Ranexa [®])	Miscellaneous cardiac drugs	-

Indications

Table 2. Food and Drug Administration (FDA) Approved Indications²

Generic Name	Indication
Ranolazine	Treatment of chronic angina

Pharmacokinetics

Table 3. Pharmacokinetics²

Generic Name	Bioavailability (%)	Protein binding (%)	Metabolism	Active Metabolites	Elimination (%)	Half-Life (hours)
Ranolazine	76	62	Mainly CYP3A4 and to a lesser extent CYP2D6	Four most abundant metabolites have half-lives of 6 to 22 hours*	Fecal (25); urinary (75)	7

*Pharmacologic activity not well characterized.

Clinical Trials

Compared to placebo, ranolazine significantly increased exercise duration, frequency of angina episodes and time to angina episodes.⁷⁻¹³ In the trial by Morrow et al, Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes (MERLIN-TIMI) 36 trial, ranolazine was compared to placebo in 6,560 patients. There was no significant difference in the primary endpoint, time to first occurrence of any element of the composite of cardiovascular death, myocardial infarction, or recurrent ischemia; however, recurrent ischemia was significantly less with ranolazine compared to placebo ($P=0.03$).¹⁴ In a subanalysis of MERLIN-TIMI 36 by Wilson et al that examined ranolazine in patients with chronic angina, significantly fewer patients in the ranolazine group compared to the placebo group experienced the primary endpoint ($P=0.017$). There was no significant difference in cardiovascular death. There was a significant decrease in recurrent ischemia with ranolazine compared to placebo ($P=0.002$).¹⁵

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Chaitman et al⁷ CARISA</p> <p>Ranolazine 750 or 1,000 mg BID in combination with diltiazem 180 mg Daily, atenolol 50 mg Daily, or amlodipine 5 mg Daily</p> <p>vs</p> <p>placebo BID in combination with diltiazem 180 mg Daily, atenolol 50 mg Daily, or amlodipine 5 mg Daily</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients with symptomatic chronic angina despite treatment with diltiazem 180 mg Daily, atenolol 50 mg Daily, or amlodipine 5 mg Daily</p>	<p>N=823</p> <p>12 weeks followed by long-term OL study of up to 39 months</p>	<p>Primary: Exercise duration on treadmill</p> <p>Secondary: Time to angina onset, time to 1 mm ST-segment depression at trough and peak, frequency of angina attacks, frequency of nitroglycerin use, survival</p>	<p>Primary: In the ranolazine group, exercise duration ($P=0.01$) was significantly increased compared to the placebo group.</p> <p>Secondary: Time to angina (P value not reported) and time to 1 mm ST-segment depression (P value not reported) were significantly increased compared to placebo.</p> <p>Treatment with ranolazine significantly reduced the frequency of angina attacks (3.3 vs 2.5 attacks per week with 750 mg; $P=0.006$; and 3.3 vs 2.1 attacks per week with 1,000 mg; $P<0.001$), and nitroglycerin use (P value not reported) compared to placebo.</p> <p>The most common adverse effects were constipation, dizziness, nausea, and asthenia ($\leq 7.3\%$ with ranolazine vs $\geq 0.7\%$ with placebo; P value not reported).</p> <p>The survival rates for patients taking ranolazine were 98.4% (95% CI, 97.4 to 99.5) at year one and 95.9% (95% CI, 94.0 to 97.7) at year two.</p>
<p>Stone et al⁸ ERICA</p> <p>Ranolazine 1,000 mg BID in combination with amlodipine 10 mg Daily</p> <p>vs</p> <p>placebo in combination with amlodipine 10 mg Daily</p>	<p>DB, PC, PG, RCT</p> <p>Stable patients with coronary disease and ≥ 3 anginal attacks per week despite maximum recommended dosage of amlodipine (10 mg/day)</p>	<p>N=565</p> <p>6 weeks</p>	<p>Primary: Frequency of angina episodes per week</p> <p>Secondary: Average weekly nitroglycerin consumption rate, SAQ, safety as assessed by adverse events and electrocardiogram</p>	<p>Primary: Angina frequency at baseline averaged 5.63 ± 0.18 episodes per week. Treatment with ranolazine significantly reduced the frequency of angina episodes per week compared to treatment with placebo (2.88 ± 0.19 vs 3.3 ± 0.22; $P=0.028$).</p> <p>Secondary: Nitroglycerin consumption use at baseline averaged 4.72 ± 0.21 tablets per week. Ranolazine treatment significantly reduced the use of nitroglycerin compared to treatment with placebo (2.03 ± 0.20 vs 2.68 ± 0.22; $P=0.014$).</p> <p>The SAQ scores on angina frequency were significantly improved with ranolazine compared to placebo ($P=0.008$). There were no significant differences between treatment groups in the other SAQ measures, such as physical limitation, anginal stability, disease perception, and treatment</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				satisfaction. Ranolazine was well tolerated.
<p>Chaitman et al⁹ MARISA</p> <p>Ranolazine 500, 1,000, or 1,500 mg BID</p> <p>vs</p> <p>placebo BID</p>	<p>DB, PC, RCT, XO</p> <p>Patients with well-documented coronary artery disease and at least a 3 month history of effort angina that responded to antianginal agents</p>	<p>N=191</p> <p>4 weeks, with long-term follow-up of up to 36 months</p>	<p>Primary: Exercise duration</p> <p>Secondary: Time to angina onset, time to 1 mm ST-segment depression at trough and peak, exercise duration at peak, long-term survival</p>	<p>Primary: Treatment with ranolazine at all doses resulted in significant increases in exercise duration ($P<0.001$).</p> <p>Secondary: Treatment with ranolazine at all doses resulted in significant increases in time to angina ($P<0.001$) and time to 1 mm ST-segment depression ($P<0.001$).</p> <p>No clinically significant changes in heart rate or blood pressure at rest or exercise were observed.</p> <p>The rates of adverse events were similar for the 500 mg and placebo groups, but higher with the 1,000 and 1,500 mg groups (15.6% for placebo, 16.0% for 500 mg, 21.7% for 1,000 mg, and 34.2% for 1,500 mg; P values not reported).</p> <p>The survival rates were 96.3% (95% CI, 93.0 to 99.5) at one year and 93.6% (95% CI, 89.3 to 98.0) at two years.</p>
<p>Rousseau et al¹⁰</p> <p>Ranolazine immediate-release* 400 mg TID for 7 to 10 days, atenolol 100 mg Daily for 7 to 10 days, and placebo Daily for 7 to 10 days</p> <p>Trial design used all 6 possible treatment sequences and each treatment period lasted 7 to 10 days.</p>	<p>DB, MC, PC, XO</p> <p>Patients with well-documented coronary artery disease and chronic angina, who were on standard doses of atenolol</p>	<p>N=158</p> <p>21 to 30 days</p>	<p>Primary: Time to onset of angina</p> <p>Secondary: Time to 1 mm ST-segment depression, total exercise duration, angina frequency, nitroglycerin use</p>	<p>Primary: Treatment with ranolazine and atenolol both resulted in significant increases in time to angina, exercise duration, and time to 1 mm ST-segment depression when compared to placebo ($P<0.05$ for all).</p> <p>Secondary: There was no significant difference between ranolazine and atenolol in the time to angina ($P=0.18$), time to 1 mm ST-segment depression ($P=0.86$), angina frequency (P value not reported) or nitroglycerin use (P value not reported). However, the increase in exercise duration was significantly greater with ranolazine than with atenolol (mean difference, 21.1 seconds; 95% CI, 6.2 to 36.0; $P=0.006$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Timmis et al¹¹</p> <p>Ranolazine 750 or 1,000 mg BID plus atenolol 50 mg Daily, diltiazem 180 mg Daily, or amlodipine 5 mg Daily</p> <p>vs</p> <p>placebo plus atenolol 50 mg Daily, diltiazem 180 mg Daily, or amlodipine 5 mg Daily</p>	<p>Posthoc analysis of CARISA trial</p> <p>Patients with chronic angina and diabetes (insulin- and non-insulin-dependent) compared to nondiabetic patients</p>	<p>N=823</p> <p>12 weeks, followed by OL extension study</p>	<p>Primary: Exercise tolerance</p> <p>Secondary: Time to onset of angina, time to ≥ 1 mm ST-segment depression, angina frequency, nitroglycerin usage, HbA1c levels in diabetic patients only and lipid panel as posthoc analysis</p>	<p>Primary: In the CARISA trial, 23% of the subjects were diabetic and 77% were not diabetic.</p> <p>The effects of ranolazine in the diabetic patients were comparable to those in the nondiabetic patients. There was no significant difference between the diabetic and nondiabetic patients in exercise duration ($P=0.89$), time to onset of angina ($P=0.54$), or time to ≥ 1 mm ST-segment depression ($P=0.44$). There was also no difference in the diabetic patients compared to the nondiabetic patients in angina frequency ($P=0.81$) or nitroglycerin consumption ($P=0.063$).</p> <p>Secondary: Compared to placebo, there were significant reductions in the HbA1c levels in with ranolazine 750 mg ($P=0.008$) and ranolazine 1,000 mg ($P=0.0002$). A subgroup analysis showed that there were significant reductions in the HbA1c levels in insulin-dependent diabetics treated with ranolazine ($P=0.016$ with 750 mg and $P=0.008$ with 1,000 mg). The non-insulin-dependent patients in the ranolazine-treated group showed a significant reduction in HbA1c with the 1,000 mg dose ($P=0.007$), but not with the 750 mg dose ($P=0.087$).</p> <p>Treatment with ranolazine 750 mg was associated with an increase in low-density lipoprotein and total cholesterol, while treatment with ranolazine 1,000 mg did not have any effects on the lipids profile (P values not reported).</p>
<p>Cocco et al¹²</p> <p>Ranolazine 10, 60, 120 or 240 mg single dose in addition to their regular antianginal medication of a β-blocker or diltiazem</p> <p>vs</p> <p>placebo in addition to</p>	<p>DB, MC, PC, RCT, XO</p> <p>Patients with chronic stable angina who remained symptomatic despite treatment with a β-blocker (atenolol, metoprolol, or</p>	<p>N=104</p> <p>4 to 9 days</p>	<p>Primary: Exercise duration, time to angina, time to 1 mm ST-segment depression</p> <p>Secondary: Heart rate, blood pressure</p>	<p>Primary: Exercise duration, time to angina and time to 1 mm ST-segment depression were significantly improved with ranolazine 240 mg dose only in the β-blocker group and the groups combined ($P<0.05$ for both). There was no significant difference in exercise duration, time to angina or time to 1 mm ST-segment depression with ranolazine treatment in the diltiazem group ($P>0.05$ for all).</p> <p>Secondary: Treatment with ranolazine did not result in significant changes in heart rate or blood pressure compared to placebo ($P>0.05$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>patient's regular β-blocker or diltiazem</p> <p>Pepine et al¹³</p> <p>Ranolazine immediate-release* 400 mg BID, 267 mg TID, or 400 mg TID</p> <p>vs</p> <p>placebo</p>	<p>propranolol) or diltiazem</p> <p>DB, MC, PC, RCT, XO</p> <p>Patients with chronic stable angina that responded to conventional antianginal therapy</p>	<p>N=312</p> <p>5 weeks</p>	<p>Primary: Time to angina onset, exercise duration, and time to 1 mm ST-segment depression at peak and trough concentrations</p> <p>Secondary: Safety</p>	<p>Primary: At peak ranolazine concentrations, time to angina onset ($P \leq 0.02$), exercise duration ($P = 0.013$), and time to 1 mm ST-segment depression (P value not reported) were significantly improved with all dosing regimens.</p> <p>At trough ranolazine concentrations, only time to 1 mm ST-segment depression was significantly improved ($P = 0.047$).</p> <p>Secondary: The rates of adverse effects were similar in the ranolazine groups and placebo group. Only minor gastrointestinal adverse effects were reported more frequently with ranolazine than placebo (6.6 to 10.7 vs 3.2%; P value not reported).</p>
<p>Koren et al¹⁶</p> <p>Ranolazine titrated to an optimal dose between 500 and 1,000 mg BID</p>	<p>MC, OL</p> <p>Patients who had completed the MARISA or CARISA trial, who were willing to participate in an OL extension</p>	<p>N=746</p> <p>Duration varied with a mean follow-up of 2.82 years</p>	<p>Primary: Discontinuation, adverse events, ECG findings, and mortality</p> <p>Secondary: Not reported</p>	<p>Primary: There were 571 patients (76.7%) that remained on therapy while 72 patients (9.7%) discontinued due to adverse events two years after initial dosing.</p> <p>There was a significant correlation between patient age >64 years and increased rates of discontinuation related to adverse events (RR, 2.32; $P < 0.001$). A significantly lower correlation of adverse event-related discontinuation was seen in patients with a history of congestive heart failure (RR, 0.55; $P = 0.030$).</p> <p>Compared to baseline, a mean prolongation of approximately 2.4 microseconds in the QT interval was observed ($P < 0.001$). However there were no significant differences in PR or QRS intervals during this time (P value not reported.). A total of 64 deaths (all causes) occurred during the 2,102 patient-years (3.0% annual incidence) of the study. This translates to a 97.2 and 94.4%, one and two-year survival from this incidence.</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Rich et al¹⁷</p> <p>Ranolazine 750 mg</p> <p>vs</p> <p>ranolazine 1,000 mg</p> <p>vs</p> <p>placebo</p> <p>Ranolazine and placebo were administered BID in combination with diltiazem 180 mg Daily, atenolol 50 mg Daily or amlodipine 5 to 10 mg Daily.</p>	<p>MA</p> <p>Patients with symptomatic chronic angina despite treatment</p>	<p>N=1,387</p> <p>6 weeks</p>	<p>Primary: Improvement in younger patients (<70 years of age) and older patients (≥70 years of age) in exercise times, angina frequency, and adverse events</p> <p>Secondary: Not reported</p>	<p>Primary: Overall ranolazine significantly improved exercise duration and time to onset of angina during exercise testing ($P \leq 0.03$).</p> <p>There was no difference in ranolazine's effect on exercise time in younger patients compared to older patients ($P > 0.8$).</p> <p>Older patients tended to have fewer angina episodes (a mean of 3.21 in the placebo group and 2.08 in the ranolazine 1,000 mg group) than younger patients (a mean of 4.16 in the placebo group and 3.11 in the ranolazine 1,000 mg group).</p> <p>Adverse events were more commonly reported in the older patients (32.6% in the placebo group and 44.2% in the ranolazine group) compared to the younger patients (31.2% in the placebo group and 32.1% in the ranolazine group).</p> <p>Secondary: Not reported</p>
<p>Morrow et al¹⁴</p> <p>MERLIN-TIMI 36</p> <p>Ranolazine 200 mg intravenously* over 1 hour, followed by an 80 mg/hour intravenous infusion* continued for 12 to 96 hours followed by 1,000 mg orally BID until study completion</p> <p>vs</p> <p>matching placebo</p> <p>Study medication was</p>	<p>DB, MC, PC, RCT</p> <p>Patients 18 years of age or older with symptoms consistent with myocardial ischemia at rest, lasting more than 10 minutes and present within the previous 48 hours and had at least 1 of the following indicators of</p>	<p>N=6,560</p> <p>Duration varied with a median follow-up of 348 days</p>	<p>Primary: Time to first occurrence of any element of the composite of cardiovascular death, myocardial infarction, or recurrent ischemia</p> <p>Secondary: Rate of major cardiovascular events (cardiovascular death, myocardial infarction, or</p>	<p>Primary: In 21.8% of the patients in the ranolazine group and 23.5% of patients in the placebo group, the primary end point occurred (HR, 0.92; 95% CI, 0.83 to 1.02; $P = 0.11$).</p> <p>In 10.4% of the patients in the ranolazine group and 10.5% of patients in the placebo group a cardiovascular death or myocardial infarction occurred (HR, 0.99; 95% CI, 0.85 to 1.15; $P = 0.87$).</p> <p>In 13.9% of the patients in the ranolazine group and 16.1% of patients in the placebo group recurrent ischemia was reduced (HR, 0.97; 95% CI, 0.76 to 0.99; $P = 0.03$).</p> <p>Secondary: Failure of therapy occurred in 36.8% of patients in the ranolazine group compared to 38.3% of patients in the placebo group (HR, 0.94; 95% CI, 0.87 to 1.02; $P = 0.16$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
administered in addition to standard therapy.	moderate to high risk of death or recurrent ischemic events: elevated biomarkers of necrosis, ST depression of at least 0.1 mV, diabetes, or a TIMI risk score for unstable angina/non-ST-elevation myocardial infarction ≥ 3		severe recurrent ischemia), rate of failure of therapy (cardiovascular death, myocardial infarction, or severe recurrent ischemia), safety (death from any cause, symptomatic arrhythmias)	<p>In 18.7% of patients in the ranolazine group compared to 19.2% of patients in the placebo group the secondary end point occurred (HR, 0.96; 95% CI, 0.86 to 1.08; $P=0.50$).</p> <p>There was no difference in the documented symptomatic arrhythmias in the ranolazine group (3.0%) and the placebo group (3.1%; $P=0.84$).</p> <p>There was no difference in the total mortality in the ranolazine group compared to the placebo group (172 vs 175; HR, 0.99; 95% CI, 0.80 to 1.22; $P=0.91$).</p>
<p>Scirica et al¹⁸ MERLIN-TIMI 36</p> <p>Ranolazine 200 mg intravenously* over 1 hour, followed by an 80 mg/hour intravenous infusion* continued for 12 to 96 hours followed by 1,000 mg orally BID until study completion</p> <p>vs</p> <p>matching placebo</p> <p>Study medication was administered in addition to standard therapy.</p>	<p>RCT</p> <p>Patients hospitalized with a non-ST-elevation acute coronary syndrome</p>	<p>N=6,560</p> <p>7 days</p>	<p>Primary: Incidence of clinically significant arrhythmias (as monitored by ECG or Holter recording performed for the first seven days after randomization)</p> <p>Secondary: Not reported</p>	<p>Primary: <i>Ventricular arrhythmias:</i> Ventricular tachycardia ≥ 3 beats ≥ 100 bpm was significantly less in the ranolazine group (52.1%) compared to the placebo group (60.6%; RR, 0.86; 95% CI, 0.82 to 0.90; $P<0.001$).</p> <p>Ventricular tachycardia ≥ 4 beats ≥ 100 bpm was significantly less in the ranolazine group (20.9%) compared to the placebo group (29.5%; RR, 0.71; 95% CI, 0.6 to 0.78; $P<0.001$).</p> <p>Ventricular tachycardia ≥ 8 beats (lasting <30 seconds) was significantly less in the ranolazine group (5.3%) compared to the placebo group (8.3%; RR, 0.63; 95% CI, 0.52 to 0.76; $P<0.001$).</p> <p>There was no significant difference in polymorphic ventricular tachycardia ≥ 8 beats in the ranolazine group (1.2%) compared to the placebo group (1.4%; RR, 0.83; 95% CI, 0.54 to 1.28; $P=0.40$).</p> <p>There was no significant difference in sustained ventricular tachycardia (≥ 30 seconds) in the ranolazine group (0.44%) compared to the placebo group</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>(0.44%; RR, 1.01; 95% CI, 0.48 to 2.13; $P=0.98$). This includes monomorphic (0.13 vs 0.22%; RR, 0.59; 95% CI, 0.17 to 2.06; $P=0.37$) and polymorphic (0.32 vs 0.22%; RR, 1.41; 95% CI, 0.52 to 3.78; $P=0.46$).</p> <p><i>Supraventricular arrhythmias:</i> There was no significant difference in new-onset atrial fibrillation in the ranolazine group (1.7%) compared to the placebo group (2.4%; RR, 0.74; 95% CI, 0.52 to 1.05; $P=0.08$).</p> <p>Other supraventricular arrhythmias ≥ 120 bpm lasting at least four beats were significantly less in the ranolazine group (44.7%) compared to the placebo group (55.0%; RR, 0.81; 95% CI, 0.77 to 0.85; $P<0.001$).</p> <p>Secondary: Not reported</p>
<p>Wilson et al¹⁵ Subanalysis of MERLIN-TIMI 36</p> <p>Ranolazine 200 mg intravenously* over 1 hour, followed by an 80 mg/hour intravenous infusion* continued for 12 to 96 hours followed by 1,000 mg orally BID until study completion</p> <p>vs</p> <p>matching placebo</p> <p>Study medication was administered in addition to standard therapy.</p>	<p>DB, MC, PC, RCT</p> <p>MERLIN-TIMI 36 patients with chronic angina</p>	<p>N=3,565</p> <p>Mean follow-up of 350 days</p>	<p>Primary: Time to first occurrence of any element of the composite of cardiovascular death, myocardial infarction, or recurrent ischemia</p> <p>Secondary: Rate of major cardiovascular events (cardiovascular death, myocardial infarction, or severe recurrent ischemia), rate of failure of therapy (cardiovascular</p>	<p>Primary: Significantly fewer patients experienced the primary endpoint in the ranolazine group compared to the placebo group (25.2 vs 29.4%; HR, 0.86; 95% CI, 0.75 to 0.97; $P=0.017$). There was no significant difference between the ranolazine and placebo groups in the risk of cardiovascular death or myocardial infarction (HR, 0.97; 95% CI, 0.80 to 1.16; $P=0.71$). Ranolazine significantly decreased the incidence of recurrent ischemia compared to placebo (HR, 0.78; 95% CI, 0.67 to 0.91; $P=0.002$).</p> <p>Secondary: Ranolazine significantly reduced the incidence of worsening angina (HR, 0.77; 95% CI, 0.59 to 1.00; $P=0.048$) and intensification of antianginal therapy (HR, 0.77; 95% CI, 0.64 to 0.92; $P=0.005$). The ranolazine group had significantly less recurrent severe ischemia compared to the placebo group (11.9 vs 14.4%; HR, 0.81; 95% CI, 0.67 to 0.98; $P=0.026$).</p> <p>In the safety endpoints, there were no significant differences between the ranolazine and placebo groups in death from any cause (HR, 1.01; 95% CI, 0.78 to 1.30; $P=0.96$), sudden cardiac death (HR, 0.81; 95% CI, 0.53 to 1.25; $P=0.35$) and symptomatic arrhythmias (HR, 0.98; 95% CI, 0.67 to 1.43; $P=0.92$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			death, myocardial infarction, or severe recurrent ischemia), safety (death from any cause, symptomatic arrhythmias)	

*The immediate-release and injectable formulations of ranolazine are not available in the United States.

Drug regimen abbreviations: BID=twice daily, TID=three times daily

Study abbreviations: DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, XO=crossover

Miscellaneous abbreviations: bpm=beats per minute, CARISA=Combination Assessment of Ranolazine in Stable Angina, CI=confidence interval, ECG=electrocardiogram, ERICA=Efficacy of Ranolazine in Chronic Angina, HbA1c=glycosylated hemoglobin A1c, HR=hazard ratio, MARISA=Monotherapy Assessment of Ranolazine in Stable Angina, MERLIN-TIMI=Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes-Thrombolysis In Myocardial Infarction, RR=relative risk, SAQ=Seattle Angina Questionnaire, TIMI=thrombolysis in myocardial infarction

Special Populations**Table 5. Special Populations²**

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Ranolazine	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Renal dose adjustment is required; plasma levels increase up to 50% in patients with renal impairment.	Contraindicated	C	Unknown

Adverse Drug Events

Ranolazine has been shown to prolong the QT interval in a dose-dependent manner. However, clinical experience in patients with acute coronary syndrome did not show an increased risk of proarrhythmia or sudden death.³

The most common adverse drug events reported with ranolazine are noted in Table 6. It is important to note that in placebo controlled trials approximately 6% of patients taking ranolazine discontinued the study medication compared to 3% of patients taking placebo. Reasons for discontinuation varied but were related to the common adverse events associated with ranolazine.²

Table 6. Adverse Drug Events²

Adverse Event	Ranolazine
Cardiovascular	
Bradycardia	0.5 to 2.0
Hypotension/orthostatic hypotension	0.5 to 2.0
Palpitations	0.5 to 2.0
QT prolongation	✓
Central Nervous System	
Confusional state	<0.5
Dizziness	6.2
Headache	5.5
Vertigo	0.5 to 2.0
Gastrointestinal	
Abdominal pain	0.5 to 2.0
Constipation	4.5
Dry mouth	0.5 to 2.0
Nausea	4.4
Vomiting	0.5 to 2.0
Hematologic	
Eosinophilia	<0.5
Hematuria	<0.5
Leukopenia	<0.5
Pancytopenia	<0.5
Thrombocytopenia	<0.5
Hematuria	<0.5

Adverse Event	Ranolazine
Renal	
Renal failure	<0.5
Serum creatinine elevations	✓
Respiratory	
Dyspnea	0.5 to 2.0
Pulmonary fibrosis	<0.5
Other	
Angioedema	<0.5
Blurred vision	<0.5
Hypoesthesia	<0.5
Paresthesia	<0.5
Peripheral edema	0.5 to 2.0
Tinnitus	0.5 to 2.0
Tremor	<0.5

✓ =Percent not specified.

Drug Interactions

Ranolazine is almost completely metabolized by the cytochrome P450 (CYP) isoenzyme system. Therefore the potential for numerous drug interactions does exist. As such, other strong CYP3A inhibitors should not be coadministered.^{3,19,20}

Table 7. Drug Interactions^{2,20}

Drug	Interaction	Mechanism
Ranolazine	Antiarrhythmic agents (amiodarone, bretylium, disopyramide, dofetilide, ibutilide, moricizine, procainamide, quinidine, sotalol)	Concurrent administration of ranolazine and antiarrhythmic agents can lead to additive effects of QT interval prolongation and therefore should be avoided. The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased.
Ranolazine	Azole antifungals (itraconazole, ketoconazole, voriconazole)	Azole antifungals are potent inhibitors of CYP3A and therefore may increase the steady-state plasma concentration of ranolazine, increasing the risk of dose-related prolongation in the QT interval, torsades de pointes–type arrhythmias, and sudden death.
Ranolazine	CYP3A4 and P-glycoprotein inducers (rifampin, rifabutin, rifapentine, phenobarbital, phenytoin, carbamazepine and St. John's Wort)	Concomitant administration may decrease the plasma concentration of ranolazine.
Ranolazine	Diltiazem	Diltiazem inhibits the metabolism of ranolazine by the CYP3A system. Concurrent administration may increase the plasma levels of ranolazine and cause QT prolongation.
Ranolazine	Grapefruit juice	Grapefruit juice inhibits the metabolism of ranolazine by the CYP3A system. Concurrent administration may increase the plasma levels of ranolazine and cause QT prolongation.
Ranolazine	Macrolide and related antibiotics (azithromycin,	Macrolide antibiotics inhibit the metabolism of ranolazine by the CYP3A system. Concomitant use may increase the plasma levels of ranolazine and cause QT prolongation.

Drug	Interaction	Mechanism
	clarithromycin, dirithromycin, erythromycin, telithromycin)	
Ranolazine	Phenothiazines (thioridazine)	There is a possible additive prolongation of the QT interval when ranolazine is administered with a phenothiazine (thioridazine). Concurrent administration may lead to additive effects on QT prolongation.
Ranolazine	Protease inhibitors (amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir)	Protease inhibitors inhibit the metabolism of ranolazine by the CYP3A system. Concurrent administration may increase the plasma levels of ranolazine and cause QT prolongation.
Ranolazine	Verapamil	Verapamil inhibits the metabolism of ranolazine by the CYP3A system. Concurrent administration may increase the plasma levels of ranolazine and cause QT prolongation.
Ranolazine	Ziprasidone	There is a possible additive prolongation of the QT interval when ranolazine is administered with ziprasidone. Concurrent administration may lead to additive effects on QT prolongation.

Dosage and Administration

Ranolazine can be taken with or without meals. It is available as an extended-release tablet which should be swallowed whole and not crushed, broken, or chewed. The maximum dose of ranolazine should be 500 mg twice daily in patients also taking diltiazem, verapamil and other moderate CYP3A inhibitors. The dose should be down-titrated in patient also taking P-glycoprotein inducers, such as cyclosporine.²

Table 8. Dosing and Administration²

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Ranolazine	<u>Treatment of chronic angina:</u> Tablet, extended-release: Initial, 500 mg twice daily; maximum, 1,000 mg twice daily	Safety and efficacy in children have not been established.	Tablet, extended-release: 500 mg 1,000 mg

Clinical Guidelines

Current guidelines are summarized in Table 9. Please note that guidelines addressing the treatment of stable angina are presented globally, addressing the role of various medication classes in the treatment of this diseases. Due to the complexity of treatment regimens for unstable angina, the associated guideline summaries focus on the role of ranolazine in disease management.

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2007 Guideline Update for the Management of Patients With Unstable Angina and Non-ST-segment Elevation Myocardial Infarction (2007)²¹	<ul style="list-style-type: none"> Sublingual nitroglycerin 0.4 mg may be used for anginal discomfort that has not been relieved by discontinuation of activity or removal from a stressful event. Doses can be repeated every five minutes if needed for three total doses. If pain persists after three doses, immediate medical attention should be sought. <p><u>Early hospital care</u></p> <ul style="list-style-type: none"> Oral β-adrenergic blocking agents (β-blockers) should be initiated within the first 24 hours unless contraindicated (i.e., patient has one or more of the following: signs of heart failure, evidence of a low-

Clinical Guideline	Recommendations
	<p>output state, increased risk of cardiogenic shock, or other relative contraindications to β-blockade).</p> <ul style="list-style-type: none"> • A nondihydropyridine calcium-channel blocker (diltiazem or verapamil) should be given as first-line treatment to patients who do not have a contraindication to either of these agents and have a contraindication to a β-blocker. These agents may also be used after β-blockers and nitrates have been fully used. • Immediate-release dihydropyridine calcium channel blockers may be considered in patients with unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI) with ongoing ischemia or hypertension in the presence of adequate β-blockade. • Angiotensin-converting enzyme (ACE) inhibitors should be administered orally to patients who do not have a contraindication within the first 24 hours to patients with congestive heart failure, diabetes, hypertension and/or left ventricular systolic dysfunction (ejection fraction <40%). If the patient is intolerant to an ACE inhibitor, an angiotensin receptor blocker (ARB) should be administered. • At the time the patient presents with UA/NSTEMI nonsteroidal anti-inflammatory drugs, except for aspirin, should be discontinued; however, β-blockers should be continued indefinitely unless contraindicated. • Ranolazine may be safely administered for symptom relief after UA/NSTEMI, but it does not appear to significantly improve underlying disease. <p><u>Late hospital care, hospital discharge, and posthospital discharge care</u></p> <ul style="list-style-type: none"> • Aspirin should be used routinely in all patients, unless contraindicated. • Clopidogrel may be used when aspirin is contraindicated or not tolerated. • Combination of aspirin and clopidogrel can be used for 12 months following UA/NSTEMI. • Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors are recommended. • Fibrates or niacin should be recommended if high-density lipoprotein <40 mg/dL, or if triglycerides are elevated. • The use of ranolazine as a component of a postdischarge regimen was not addressed. <p>Note: A focused update to the 2007 guideline was published in 2011; however, the recommendations above were not updated and remain current to the 2007 guideline.²²</p>
<p>American College of Cardiology /American Heart Association: 2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable Angina (2007)⁴³</p>	<ul style="list-style-type: none"> • Aspirin should be started at 75 to 162 mg/day and continued indefinitely in all patients, unless contraindicated. • Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely. • Patients with hypertension and established coronary artery disease should be treated with blood pressure medication(s) as tolerated, including (ACE inhibitors and/or β-blockers with the addition of other medications as needed to achieve blood pressure goals of <140/90 or <130/80 mm Hg for patients with chronic kidney disease or

Clinical Guideline	Recommendations
	<p>diabetes.</p> <ul style="list-style-type: none"> • Long-acting calcium-channel blocking agents or long-acting nitrates may be used if β-blockers are contraindicated. Immediate-release and short-acting dihydropyridine calcium channel blockers can increase adverse cardiac events and should not be used. • Long-acting calcium channel blockers or long-acting nitrates may be used with β-blockers if initial treatment is not successful. • ACE inhibitors should be used indefinitely in patients with a left ventricular ejection fraction (LVEF) of $\leq 40\%$ and in those with hypertension, diabetes or chronic kidney disease, unless contraindicated. • ACE inhibitors should also be used indefinitely in patients at lower risk (mildly reduced or normal LVEF in whom cardiovascular risk factors remain well controlled and revascularization has been performed), unless contraindicated. • ARBs are recommended in patients with hypertension, those who have an indication for an ACE inhibitor and are intolerant to them, who have heart failure, or who have had a myocardial infarction and have a LVEF of $\leq 40\%$. • ARBs may be considered in combination with an ACE inhibitor for heart failure due to left ventricular systolic dysfunction. • Aldosterone blockade is recommended in patients post-myocardial infarction without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and a β-blocker, have a LVEF $\leq 40\%$ and have either diabetes or heart failure. • It is beneficial to start and continue β-blocker therapy indefinitely in all patients who have had a myocardial infarction, acute coronary syndrome or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated. • Annual influenza vaccination is recommended in patients with cardiovascular disease. • The use of ranolazine for the treatment of angina was not addressed.
<p>European Society of Cardiology: Management of Stable Angina Pectoris (2006)²⁴</p>	<p><u>Therapy to improve prognosis</u></p> <ul style="list-style-type: none"> • Aspirin 75 mg once daily is recommended in all patients without contraindications. • Statin therapy is recommended for all patients with coronary disease. • ACE inhibitor therapy is recommended for patients with indications for ACE inhibition including hypertension, heart failure, left ventricular dysfunction and history of myocardial infarction with left ventricular dysfunction and diabetes. • β-blocker therapy is recommended in patients with history of myocardial infarction or heart failure. • Class IIa evidence includes ACE inhibition in patients with angina and proven coronary disease, clopidogrel in patients with stable angina who are not candidates for aspirin and high dose statin therapy in high risk patients with proven coronary disease. • Class IIb evidence includes fibrates in patients with low high density lipoprotein cholesterol and high triglycerides who have diabetes or metabolic syndrome. • Calcium channel blockers may be recommended in patients with

Clinical Guideline	Recommendations
	<p>angina who cannot tolerate β-blockers and who have had a myocardial infarction and who do not have heart failure.</p> <p><u>Therapy to improve symptoms and/or reduce ischemia</u></p> <ul style="list-style-type: none"> • Short-acting nitroglycerin therapy is recommended for acute symptom relief and situational prophylaxis. • Test the effects of a β_1 blocker and titrate to full dose; consider the need for 24-hour protection against ischemia. • If β-blockers are not effective or not tolerated, attempt monotherapy with a calcium channel blocker, long-acting nitrate or nicorandil*. • If the effects of β-blocker therapy are insufficient, add a dihydropyridine calcium channel blocker. • Class IIa evidence includes a sinus node inhibitor in the case of β-blocker intolerance, or a long-acting nitrate or nicorandil* in place of a calcium channel blocker in the case of insufficient response to calcium channel blocker monotherapy or combination therapy with a calcium channel blocker and β-blocker. • Class IIb evidence includes the use of metabolic agents where available as add-on therapy or in place of conventional therapy when conventional therapy is not tolerated. <p><u>Treatment of syndrome X</u></p> <ul style="list-style-type: none"> • Therapy with nitrates, β-blockers and calcium channel blockers alone or in combination is recommended. • Statin therapy is recommended in patients with hyperlipidemia. • ACE inhibitors are recommended in patients with hypertension. • Class IIa evidence includes a trial of other anti-anginal agents such as nicorandil and metabolic agents. <p><u>Treatment of vasospastic angina</u></p> <ul style="list-style-type: none"> • Treatment with calcium channel blockers is recommended in patients whose coronary arteriogram is normal or shows only non-obstructive lesions. • No recommendations were made regarding the use of ranolazine.
<p>European Society of Cardiology: European Society of Cardiology: Guidelines for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes (2007)²⁵</p>	<ul style="list-style-type: none"> • β-Blockers are recommended in the absence of contraindications, particularly in patients with hypertension or tachycardia and are usually well tolerated. • Intravenous or oral nitrates are effective for symptom relief in the acute management of anginal episodes. • Calcium channel blockers provide symptom relief in patients already receiving nitrates and β-blockers; they are useful in patients with contraindications to β-blockade and in the subgroup of patients with vasospastic angina. • Nifedipine, or other dihydropyridines, should not be used unless combined with β-blockers. • It is noted that ranolazine exerts antianginal effects by inhibiting the late sodium current and that it was not effective in reducing major cardiovascular events in Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes trial. • The use of ranolazine for the treatment of angina was not further addressed.

*Agent not available in the United States.

Conclusions

Ranolazine is an antianginal drug that has been shown to significantly improve exercise duration, time to onset of angina, and time to 1 mm ST-segment depression. It also reduces angina frequency and nitroglycerin use.⁸⁻¹⁰ Ranolazine is Food and Drug Administration (FDA) approved for chronic angina.²

Ranolazine has a different mechanism of action than currently available agents to treat angina and does not cause hemodynamic changes such as reduction in blood pressure or heart rate.³ The most common adverse effects were dizziness, nausea, asthenia, and constipation.² A significant concern with ranolazine is its potential for QT prolongation.¹ Therefore, ranolazine should be avoided in patients with pre-existing QT prolongation, who are taking QT-prolonging drugs or strong CYP3A inhibitors or patients with any type of hepatic impairment or severe renal impairment.²

Most current guidelines do not address the use of ranolazine, as it was approved after their publication.^{23,25} The American College of Cardiology/American Heart Association guideline on unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI), states that when used in accordance with its FDA-approved indication, ranolazine may be safely administered for symptom relief after UA/NSTEMI but it does not appear to significantly improve underlying disease.²¹ The European Society of Cardiology (ESC) does mention ranolazine in their Management of Stable Angina Pectoris guideline but no recommendations were issued concerning its use.²⁴ The ESC notes in their Management of Acute Coronary Syndrome in Patients Presenting Without Persistent ST-segment Elevation guideline that ranolazine exerts antianginal effects by inhibiting the late sodium current and that it was not effective in reducing major cardiovascular events in the Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes trial.²⁵

Currently there is limited data comparing ranolazine to other currently available antianginal agents such as β -blockers, calcium channel blockers, and long-acting nitrates. In one trial, Rousseau and colleagues demonstrated that the immediate-release formulation of ranolazine, when compared to atenolol, increased exercise duration. However, ranolazine proved similar to atenolol in its effect on other anginal symptoms such as time to angina, time to 1 mm ST-segment depression, angina frequency, and nitroglycerin use.¹⁰

Appendix I: Utilization Within This Drug Class for DVHA: April 1, 2011 to June 30, 2011

Medication	# of Rx's	Market Share (%)	Plan Cost \$	Avg \$/Rx
Ranexa	34	100%	\$9,993.72	\$293.93
Class Total:	34	100%	\$9,993.72	\$293.93

Recommendations

No changes to the Department of Vermont Health Access (DVHA) approval criteria for miscellaneous cardiac drugs (see below) are proposed.

Ranexa[®]:

- The patient has had a diagnosis/indication of chronic angina.
- AND**
- The patient has had a documented side effect, allergy, or treatment failure with at least one medication from two of the following classes: beta-blockers, maintenance nitrates, or calcium channel blockers.
- AND**
- The patient does not have any of the following conditions:
 - Hepatic insufficiency
 - Concurrent use of medications which may interact with Ranexa[®]:
 - CYP450 3A4 inducers (rifampin, rifabutin, rifapentin, phenobarbital, phenytoin, carbamazepine, St.John's wort)
 - CYP450 3A4 inhibitors (diltiazem, verapamil, ketoconazole, protease inhibitors, grapefruit juice, macrolide antibiotics)

- Note: doses of digoxin or drugs metabolized by CYP450 2D6 (TCAs, some antipsychotics) may need to be adjusted if used with Ranexa[®].
AND
- The dose requested does not exceed 3 tablets/day (500 mg) or 2 tablets/day (1000 mg).

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