**ABSTRACT**

**OBJECTIVE:** To describe the approved uses, pharmacology, pharmacodynamics, pharmacokinetics, efficacy, safety, and place in therapy of ranolazine, the first new antianginal drug therapy introduced in more than 20 years for the treatment of chronic angina.

**SUMMARY:** The mechanism of action of ranolazine is unknown, but it may involve inhibition of the late sodium current in the myocardium, thereby preventing sodium-induced intracellular calcium overload during ischemia. This mechanism differs from that of other antianginal agents, which primarily affect myocardial oxygen supply or demand through hemodynamic effects. Ranolazine undergoes extensive metabolism, primarily by cytochrome P-450 (CYP) 3A4, so interactions with drugs that are moderate to potent inhibitors of CYP3A4 need to be considered. Ranolazine is also a P-glycoprotein (P-gp) substrate and inhibitor, and it may interact with other P-gp substrates and inhibitors. In patients with an inadequate response to other antianginal agents, the addition of ranolazine to existing antianginal therapy increases exercise duration and the time to angina on an exercise treadmill test, and it decreases the frequency of angina attacks and nitroglycerin use. The drug produces antianginal effects without significantly affecting either heart rate or blood pressure. Ranolazine prolongs the QT interval on the electrocardiogram, but the overall electrophysiologic effects of the drug suggest that it is not expected to cause torsades de pointes.

**CONCLUSION:** Ranolazine has a unique mechanism of action that may be complementary to that of conventional antianginal agents in the treatment of chronic angina. An understanding of the potential for drug interactions, disease interactions, and contraindications is needed to ensure safe and effective use of the drug.

**KEYWORDS:** Drug interactions, Electrophysiologic effects, Pharmacotherapy, Ranolazine, Stable angina

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**Pharmacology**

Despite documented efficacy in reducing the burden of angina, conventional antianginal agents (i.e., beta-blockers, calcium channel blockers, long-acting nitrates) are limited by contraindications (e.g., beta-blockers in asthma), as well as intolerance because of side effects or adverse hemodynamic manifestations. While revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) effectively reduces the number of anginal attacks, not all patients will receive complete relief. In addition, many patients are not candidates for revascularization therapy even when they experience continued anginal attacks while on aggressive medical therapy with conventional antianginal agents. Given the limitations with current treatment options for angina, there is a clear need for new therapies, particularly therapies without the limitations of conventional antianginal medications. Ranolazine, the first new antianginal drug introduced in more than 20 years, appears to be such an agent.

Ranolazine was approved by the U.S. Food and Drug Administration (FDA) in January 2006 for the treatment of chronic angina in combination with amiodipine, beta-blockers, or nitrates.¹ Ranolazine is not indicated for monotherapy at this time and should be reserved for patients with an inadequate response to other antianginal drugs.² Ranolazine, available as 500 mg extended-release tablets, should be initiated at a dose of 500 mg twice daily and may be titrated up to 1,000 mg twice daily as needed based on clinical symptoms.³

Conventional antianginal agents reduce myocardial oxygen demand, usually by decreasing heart rate and blood pressure or by increasing myocardial oxygen supply as a result of coronary vasodilation (see the preceding article by Dobesh in this supplement). Unlike most other antianginal agents, the antianginal effect of ranolazine does not depend on a reduction in heart rate or blood pressure.¹²

While it is established that ranolazine does not significantly affect hemodynamics, recent work has potentially identified its mechanism of action. In the past, ranolazine was thought to maintain myocardial function during ischemia by inhibiting fatty acid oxidation and shifting myocardial energy production from fatty acid oxidation to glucose oxidation, which produces a higher amount of adenosine triphosphate per oxygen molecule consumed.¹ However, these effects are observed only at plasma concentrations that far exceed those achieved with doses used clinically. Therefore, at this time, metabolic modulation does not appear to play a significant role in the relief of angina by ranolazine.²⁴ More recent clinical evidence indicates that the antianginal effect of ranolazine may involve an electrophysiologic mechanism.

Depolarization of myocardial cell membranes is initiated by the rapid influx of sodium ions into the myocardial cell through
sodium channel openings. Within milliseconds of this rapid influx of sodium into the cell, sodium channels are rapidly inactivated through a gating mechanism. However, under normal conditions, a certain percentage of sodium channels fail to inactivate, resulting in a small but detectable late sodium current during the plateau phase of the action potential. Recent investigations indicate that this late sodium current is augmented in pathologic conditions such as ischemia or heart failure. This increase in intracellular sodium ultimately results in an increase in intracellular calcium, likely through the reverse mode of the sodium-calcium exchanger. Elevated intracellular calcium results in myocardial dysfunction, as well as increased left ventricular diastolic wall stiffness (i.e., increased myocardial oxygen demand). Additionally, elevated wall tension causes extravascular compression of coronary vessels, which may decrease oxygen supply to the myocardium. These effects may create a cycle of progressively worsening ischemia.

Recent animal studies have identified that, at clinically relevant plasma concentrations, ranolazine selectively inhibits late sodium entry into the cell without significantly affecting the rapid upstroke of sodium at the onset of the action potential. Consequently, ranolazine would be expected to prevent consequences of ischemia, such as myocardial dysfunction, elevated wall tension, and reduced oxygen supply. In fact, based on this proposed mechanism, ranolazine would be expected to produce greater clinical benefit in patients with more severe or frequent angina. It is important to note that conventional antianginal agents work to prevent myocardial ischemia from developing through restoration of the balance between myocardial oxygen supply and demand. Because ranolazine would be expected to prevent the consequences of ischemia once it develops, the drug should be an effective complement to conventional antianginal agents in treating patients with chronic stable angina.

### Pharmacokinetics

Ranolazine is rapidly and extensively metabolized in the intestine and liver, and its absorption is variable. Peak plasma concentrations of ranolazine are reached 2 to 5 hours after oral administration of the extended-release formulation. The bioavailability of extended-release tablets is 76% compared with oral ranolazine solution. Food does not have a clinically important effect on the peak plasma concentration or area under the plasma concentration-time curve (AUC) of ranolazine. Therefore, the drug may be taken with or without meals.

The apparent terminal half-life of ranolazine is 7 hours. Steady-state ranolazine plasma concentrations are achieved within 3 days of twice-daily dosing with the extended-release preparation. The peak-to-trough ranolazine plasma concentration ratio is 1.6 to 3.0, suggesting that the drug will produce relatively consistent therapeutic effects throughout the dosing interval. At steady-state and therapeutic dosages, the relationship between dosage and both peak plasma concentration and AUC is nearly linear, but these pharmacokinetic measures increase slightly more than proportionally to the dosage. Ranolazine is approximately 62% bound to plasma proteins (primarily α1-acid glycoprotein) at therapeutic plasma concentrations.

Ranolazine undergoes extensive metabolism in the liver and intestine, with less than 5% of an oral dose excreted unchanged in the urine and feces. After a single oral dose of ranolazine oral solution, approximately 75% of the dose was excreted in the urine and 25% was excreted in the feces. Ranolazine is metabolized primarily by cytochrome P-450 (CYP) 3A4 and to a lesser extent (10% to 15% of a given dose) by CYP2D6. It is unknown whether the metabolites of ranolazine are pharmacologically active.

### Clinical Trials

Initial studies with ranolazine utilized an immediate-release formulation dosed 3 times a day. While these studies did produce favorable results for ranolazine in terms of increasing exercise tolerance at peak concentrations, the peak-to-trough ratio was unfavorable. Subsequently, the efficacy of the extended-release formulation of ranolazine in the treatment of patients with chronic stable angina was demonstrated in 3 pivotal phase 3 clinical trials. Participants in these studies were primarily white, mostly male, with an average age between 60 and 65 years. As would be expected of patients with chronic stable angina, many patients had a history of diabetes mellitus, heart failure, hypertension, myocardial infarction (MI), and PCI or CABG.

### Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) Study

The MARISA study was a randomized, double-blind, placebo-controlled, 4-period crossover study of 191 adults with coronary artery disease (CAD) and angina. Patients were eligible for the study if they had at least a 3-month history of stable angina that responded to either beta-blockers, calcium channel blockers, or long-acting nitrates. Upon discontinuation of their current antianginal medications, patients were enrolled if they developed exercise-limiting angina or electrocardiogram (ECG) changes indicative of ischemia on 2 exercise treadmill tests. Patients were randomly assigned to receive extended-release ranolazine 500 mg, 1,000 mg, 1,500 mg, or placebo orally twice daily for 1 week (ranolazine monotherapy is not approved by the FDA, but it was used in this study). Overall, the study had 4 treatment periods, with each patient crossing over to each treatment arm in a random fashion. At the end of each week of treatment, exercise treadmill testing was performed at 4 hours and 12 hours after drug administration, times that correspond to peak and trough ranolazine plasma concentrations.

The average patient was aged 64 years, 73% of the patients were male, and 91% of patients were white. The primary efficacy analysis included 175 patients who completed 3 of the 4 treatment periods. At both times corresponding to trough and peak plasma ranolazine concentrations, all 3 ranolazine dosages
After 2 weeks of treatment, the exercise duration or time to angina was significantly increased by both ranolazine dosages compared with placebo at the times corresponding to both peak and trough plasma drug concentrations. The time to 1 mm ST-segment depression on the ECG was significantly increased by both ranolazine dosages compared with placebo only at the time of peak plasma drug concentration (Table 2). All improvements were sustained over the 12 weeks of therapy.

At the time of trough plasma ranolazine concentrations, the average exercise duration was 24 seconds longer with both ranolazine dosages than with placebo, and the average time to angina was 26 to 30 seconds longer with ranolazine than with placebo. The magnitude of increase in exercise duration or time to angina is comparable with those observed in studies of conventional antianginal agents, although studies directly comparing ranolazine with conventional agents are needed.12,13

Ranolazine also demonstrated benefits in other clinical end points. At baseline, the average number of angina attacks per week was 4.5.10 After 12 weeks of treatment, the frequency of angina was reduced to a significantly greater extent by both ranolazine dosages than by placebo. The average number of attacks per week was 3.3 in the placebo group, 2.5 in the ranolazine 750 mg twice-daily group, and 2.1 in the ranolazine 1,000 mg twice-daily group after 12 weeks of treatment. The average number of sublingual nitroglycerin doses used per week after 12 weeks of treatment also was significantly lower in both ranolazine groups (2.1 with 750 mg twice daily and 1.8 with 1,000 mg twice daily) compared with the placebo group (3.1).

**Table 1: Main Results From the MARISA Trial**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Placebo</th>
<th>Ranolazine 500 mg BID</th>
<th>Ranolazine 1,000 mg BID</th>
<th>Ranolazine 1,500 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean peak/ trough exercise duration (seconds)</td>
<td>501.7/505.7</td>
<td>531.0/529.5 (P&lt;0.001)</td>
<td>551.8/539.4 (P&lt;0.001)</td>
<td>571.2/551.6 (P&lt;0.001)</td>
</tr>
<tr>
<td>Mean peak/ trough time to angina (seconds)</td>
<td>416.3/407.3</td>
<td>451.8/434.3 (P&lt;0.005)</td>
<td>472.7/453.2 (P&lt;0.001)</td>
<td>484.8/466.9 (P&lt;0.001)</td>
</tr>
<tr>
<td>Mean peak/ trough time to 1 mm ST-segment depression (seconds)</td>
<td>436.4/443.4</td>
<td>485.2/471.0 (P&lt;0.001)</td>
<td>492.0/487.9 (P&lt;0.001)</td>
<td>505.4/508.0 (P&lt;0.001)</td>
</tr>
</tbody>
</table>

**Table 2: Main Results from the CARISA Trial**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Placebo 750 mg BID</th>
<th>Ranolazine 750 mg BID</th>
<th>Ranolazine 1,000 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean peak/ trough exercise duration (seconds)</td>
<td>531.9/510.0</td>
<td>564.2/531.8 (P=0.001)</td>
<td>561.9/532.5 (P=0.02)</td>
</tr>
<tr>
<td>Mean peak/ trough time to angina (seconds)</td>
<td>479.1/441.0</td>
<td>514.7/468.7 (P=0.002)</td>
<td>510.4/467.0 (P=0.003)</td>
</tr>
<tr>
<td>Mean peak/ trough time to 1 mm ST-segment depression (seconds)</td>
<td>463.5/424.0</td>
<td>485.2/471.0 (P&lt;0.01)</td>
<td>494.2/447.8 (P=0.004)</td>
</tr>
</tbody>
</table>

**Combination Assessment of Ranolazine in Stable Angina (CARISA) Study**

The CARISA study was a randomized, double-blind, placebo-controlled, parallel-group trial of 823 adults with symptomatic chronic angina despite treatment with conventional antianginal drug therapy.10 Eligibility and enrollment criteria were similar to the MARISA study except that patients in the CARISA study were allowed to continue on monotherapy with fixed doses of atenolol 50 mg/day, amiodipine 5 mg/day, or extended-release diltiazem 180 mg/day. Patients were randomly assigned to receive extended-release ranolazine 750 mg or 1,000 mg or placebo orally twice daily as add-on therapy for 12 weeks. Sublingual nitroglycerin was allowed. Exercise treadmill testing was performed 4 hours after drug administration after 2 weeks and 12 weeks of treatment, and 12 hours after drug administration after 2 weeks, 6 weeks, and 12 weeks of treatment.

The average patient was aged 64 years, and roughly 3 out of 4 patients were male.10 After 2 weeks of treatment, the exercise duration and time to angina were significantly increased by both ranolazine dosages compared with placebo at the times corresponding to both peak and trough plasma drug concentrations. The time to 1 mm ST-segment depression on the ECG was significantly increased by both ranolazine dosages compared with placebo only at the time of peak plasma drug concentration (Table 2). All improvements were sustained over the 12 weeks of therapy.
Ranolazine demonstrated minimal effects on blood pressure and heart rate.10 Dose-related adverse effects from ranolazine were similar to those reported in the MARISA study.10 Tolerance to ranolazine did not develop during the 12 weeks of treatment.1

Long-term survival rates in patients continuing ranolazine in an open-label extension of the CARISA study were similar to those reported in the open-label extension of the MARISA study. The survival rate was 98.4% in 480 patients who continued taking ranolazine for 1 year and 95.9% in 173 patients who continued the drug for 2 years.10

**Efficacy of Ranolazine in Chronic Angina (ERICA) Study**

The multicenter, randomized, placebo-controlled, parallel-group ERICA study involved 565 patients with chronic angina.2,11 After a 2-week qualifying phase in which an oral placebo was given twice daily along with amlodipine 10 mg/day (the maximum recommended dosage for treating angina), patients with 3 or more anginal attacks per week were randomly assigned to receive extended-release ranolazine 500 mg or placebo orally twice daily for 1 week, followed by titration to ranolazine 1,000 mg or placebo twice daily as tolerated over the subsequent 6-week double-blind treatment phase. Patients randomized to placebo for the first week received placebo for the subsequent 6 weeks (i.e., there was no crossover between treatments). Amlodipine was continued throughout the study in both treatment groups. Sublingual nitroglycerin was used as needed to treat angina episodes. Long-acting nitrates were used in conjunction with amlodipine in 43% of patients randomized to placebo, and 46% of patients randomized to ranolazine therapy.11

The characteristics of the 2 treatment groups (ranolazine and placebo) were similar at baseline.11 The mean age was 62 years, 72% of patients were male, and 99% were white.11 Most patients (89%) had hypertension, 80% had a history of MI, 51% had congestive heart failure, 23% were current smokers, and 19% had diabetes mellitus.11 The average frequency of angina attacks (5.6 attacks per week) and nitroglycerin consumption (4.6 times per week) were similar in the 2 groups despite the use of amlodipine in all patients and long-acting nitrates in nearly half of patients.

At the end of the 6-week treatment phase, the average weekly number of angina attacks had decreased to a significantly greater extent in the ranolazine group (to 2.88) than in the placebo group (to 3.31).11 A significantly greater decrease in the average number of times weekly that nitroglycerin was used was also observed in the ranolazine group (to 2.03) than in the placebo group (to 2.68).11 These effects appeared consistent regardless of patient age (less than 65 years versus 65 years or older) and use of long-acting nitrates.2,11 Stratification of the angina frequency and nitroglycerin use data by baseline angina severity revealed that ranolazine had a greater impact in patients with more angina attacks at baseline.11

Similar to previous trial experience, ranolazine was well tolerated in the ERICA study, with most adverse effects classified as mild or moderate in severity.11 The most common increase in adverse effects with ranolazine compared with placebo were constipation (8.9% versus 1.8%), dizziness (3.9% versus 2.5%), nausea (2.8% versus 0.7%), and headache (2.8% versus 2.5%).14 There were no significant changes from baseline in supine or standing systolic or diastolic blood pressure or heart rate measurements in either treatment group.11

**Safety**

More than 3,300 patients received ranolazine in clinical trials, including nearly 1,200 patients who received the drug in the 3 pivotal phase 3 clinical trials, for a total of 2,710 patient-years of exposure to the drug.1,9,10,11 In open-label study extensions, 639 patients were exposed to ranolazine for more than 1 year, 578 patients were exposed to the drug for more than 2 years, and 372 patients were exposed for more than 3 years.1

While the effect of ranolazine on long-term mortality is not known and is the focus of ongoing studies, currently available information does not demonstrate an adverse effect on mortality from the drug. In the CARISA study, the longest of the 3 pivotal phase 3 studies, 3 (1%) of 269 placebo-treated patients, 2 (0.7%) of 279 patients in the ranolazine 750 mg twice-daily group, and 1 (0.4%) of 275 patients in the ranolazine 1,000 mg twice-daily group died during the study.10 Previously reported survival rate data from the open-label portions of the MARISA and CARISA studies also suggest that ranolazine does not have an adverse effect on survival.1,10 In controlled studies, the rate of discontinuation of the study drug because of adverse effects was 6% with ranolazine and 3% with placebo.1

**Disease and Drug Interactions**

Ranolazine interactions with various diseases and drugs are well characterized. Mild, moderate, and severe hepatic impairment (Child-Pugh classes A, B, and C) are contraindications to the use of extended-release ranolazine.1 The plasma concentrations of ranolazine were increased 1.3- and 1.6-fold in patients with mild (Child-Pugh class A) and moderate (Child-Pugh class B) hepatic impairment, respectively, compared with healthy volunteers.1

Renal impairment is not a contraindication to the use of extended-release ranolazine. Nevertheless, the drug should be used with caution in this patient population, especially patients with severe renal impairment. The pharmacokinetics of extended-release ranolazine (an 875 mg loading dose followed by four 500 mg doses every 12 hours) were evaluated in 8 healthy subjects and 21 subjects with mild-to-severe renal impairment.1 At steady state, the ranolazine AUC for the 12-hour period after drug administration was increased by 72%, 80%, and 97% in subjects with mild, moderate, and severe renal impairment, respectively, compared with the healthy subjects. Since plasma concentrations of ranolazine may increase by 50% in patients with varying degrees of renal impairment,1 careful assessment of patient response and tolerability should take place prior to dose titration, and 500 mg twice daily may represent the maximum dose that...
These Several QT Interval Prolongation Diltiazem 180 mg/day and 360 mg/day Ranolazine has been shown to The relationship between QT prolongation and However, no adjustment in extended-Verapamil is a Less potent CYP3A4 A 2-fold increase in plasma concentrations of simvas-## 

The drug causes a reduction in the net repolarizing current, which results in prolongation of the ventricular action potential duration (APD). Resulting early after-depolarizations (EADs) generate ectopic beats that might serve as a trigger to initiate reentry to perpetuate TdP (there is less consensus for this mechanism). Dispersion of ventricular repolarization refers to the differences in action potential duration (DAPD) across the left ventricular wall (transmural), between the left and right ventricles, or between the base and apex of the heart. The increase in spatial dispersion of ventricular repolarization leads to heterogeneity of refractoriness, which serves as a substrate for reentry. Dashed arrows indicate pathways (mechanisms) with currently less supportive evidence than those indicated by solid arrows.

Early After-Depolarizations (EADs) Diltiazem, verapamil, macrolide antibiotics, protease inhibitors for the treatment of human immunodeficiency virus, grapefruit juice) Ranolazine is contraindicated in patients receiving drugs that cause QT prolongation have been associated with proarrhythmia, specifically torsades de pointes, and sudden cardiac death. The relationship between QT prolongation and proarrhythmia has not been studied in patients receiving ranolazine, but the possibility of additive prolongation of the QT interval and a higher incidence of proarrhythmia should be considered when ranolazine is used in a patient who has preexisting QT interval prolongation, is receiving another drug that prolongs the QT interval, or has an elevated risk for torsades de pointes (e.g., uncorrected hypokalemia or hypomagnesemia).

**FIGURE 1** Electrophysiologic Events and Genesis of Torsades de Pointes

Net Repolarization Current

Prolongation of Action Potential Duration

Increased Dispersion of Ventricular Repolarization (ΔAPD)

Ectopic Beats

Early After-Dopolarizations (EADs)

Triggered Activity

Trigger

Reentry

Perpetuator

Torsades de Pointes

Perpetuator

Net Repolarization Current

Prolongation of Action Potential Duration

Increased Dispersion of Ventricular Repolarization (ΔAPD)

Ectopic Beats

Early After-Dopolarizations (EADs)

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Perpetuator

The drug causes a reduction in the net repolarizing current, which results in prolongation of the ventricular action potential duration (APD). Resulting early after-depolarizations (EADs) generate ectopic beats that might serve as a trigger to initiate reentry to perpetuate TdP (there is less consensus for this mechanism). Dispersion of ventricular repolarization refers to the differences in action potential duration (DAPD) across the left ventricular wall (transmural), between the left and right ventricles, or between the base and apex of the heart. The increase in spatial dispersion of ventricular repolarization leads to heterogeneity of refractoriness, which serves as a substrate for reentry. Dashed arrows indicate pathways (mechanisms) with currently less supportive evidence than those indicated by solid arrows.


The pharmacokinetics of ranolazine in patients receiving dialysis have not been evaluated. Blood pressure should be monitored regularly after initiating ranolazine in patients with severe renal impairment because the mean diastolic blood pressure increased approximately 10 to 15 mm Hg in 6 subjects with severe renal impairment who received 500 mg twice daily.

Concurrent use of ranolazine with diltiazem and other potent or moderately potent CYP3A4 inhibitors is contraindicated because ranolazine is metabolized primarily by CYP3A4. These CYP3A4 inhibitors (e.g., ketoconazole, other antifungal agents, diltiazem, verapamil, macrolide antibiotics, protease inhibitors for the treatment of human immunodeficiency virus, grapefruit juice) can substantially increase ranolazine plasma concentrations.

Ketoconazole 200 mg twice daily increased average plasma ranolazine concentrations more than 3-fold when it was administered concurrently with extended-release ranolazine 1,000 mg twice daily.

Diltiazem 180 mg/day and 360 mg/day increased steady-state plasma ranolazine concentrations 1.8-fold and 2.3-fold, respectively, when diltiazem was used concomitantly with ranolazine 1,000 mg twice daily.

Less potent CYP3A4 inhibitors (e.g., cimetidine) do not increase plasma concentrations of ranolazine and are not contraindicated during ranolazine therapy.

Verapamil 120 mg 3 times daily doubled steady-state plasma ranolazine concentrations when used concurrently with extended-release ranolazine 750 mg twice daily. Verapamil is a P-glycoprotein (P-gp) inhibitor as well as an inhibitor of CYP3A4. In vitro studies indicate that ranolazine is a P-gp substrate. Verapamil and other P-gp inhibitors (e.g., ritonavir, cyclosporine) may increase ranolazine absorption and bioavailability. Ranolazine also inhibits P-gp, and the dosage of other P-gp substrates (e.g., digoxin, simvastatin) may need to be reduced when ranolazine is used concurrently. Coadministration of extended-release ranolazine (1,000 mg twice daily) and digoxin 0.125 mg/day increased plasma digoxin concentrations approximately 1.5-fold. A 2-fold increase in plasma concentrations of simvastatin and its active metabolite were observed when extended-release ranolazine 1,000 mg twice daily and simvastatin 80 mg/day were used concomitantly.

Steady-state ranolazine plasma concentrations were increased 1.2-fold when 20 mg/day of paroxetine, a potent CYP2D6 inhibitor, and extended-release ranolazine 1,000 mg twice daily were used simultaneously. However, no adjustment in extended-release ranolazine dosage is required when the drug is used with paroxetine or other CYP2D6 inhibitors because CYP2D6 plays a limited role in ranolazine metabolism. However, ranolazine may inhibit the activity of CYP2D6 and the metabolism of certain other drugs (e.g., tricyclic antidepressants, some antipsychotic agents) by this isoenzyme. Although ranolazine can also inhibit CYP3A4, ranolazine and its most abundant metabolites are not known to inhibit the metabolism of substrates for CYP1A2, 2C9, 2C19, or 2E1.

**QT Interval Prolongation** Ranolazine is contraindicated in patients receiving drugs that prolong the QT interval on the ECG, including class Ia antiarrhythmic agents (e.g., quinidine), class III antiarrhythmic agents (dofetilide, sotalol), erythromycin, and certain antipsychotic agents (e.g., thioridazine, ziprasidone), and in patients with pre-existing QT interval prolongation. Ranolazine has been shown to prolong the QT interval corrected for heart rate (QTc) in a dose- and plasma-concentration-related manner. Several agents that cause QT prolongation have been associated with proarrhythmia, specifically torsades de pointes, and sudden cardiac death. The relationship between QT prolongation and proarrhythmia has not been studied in patients receiving ranolazine, but the possibility of additive prolongation of the QT interval and a higher incidence of proarrhythmia should be considered when ranolazine is used in a patient who has preexisting QT interval prolongation, is receiving another drug that prolongs the QT interval, or has an elevated risk for torsades de pointes (e.g., uncorrected hypokalemia or hypomagnesemia).
A baseline ECG should be obtained before initiating ranolazine. The relationship between change in QTc interval and ranolazine plasma concentration is well established. At ranolazine plasma concentrations up to 4 times higher than those associated with the maximum recommended dosage, the relationship is linear with a slope of about 2.6 msec per 1,000 ng/mL. The slope is steeper in patients with hepatic impairment, with 3-fold greater increases in QTc interval prolongation for each increment in plasma concentration compared with patients without hepatic impairment. In patients without hepatic impairment, the average QTc interval prolongation is 6 msec at the maximum recommended dosage, although a prolongation of at least 15 msec has been observed in the 5% of the population with the highest plasma concentrations.

Drugs that produce QT prolongation immediately raise concern in clinicians that the risk of proarrhythmia may be increased. However, it is well established that not every agent that produces QT prolongation is associated with an elevated risk for proarrhythmia. Although torsades de pointes is associated with some drugs that prolong the QT interval (e.g., dofetilide), the incidence of torsades de pointes is low in patients treated with other drugs that cause QT interval prolongation (e.g., amiodarone). Thus, a better surrogate measure of the proarrhythmic potential of drug therapies is needed.

Recent work indicates that prolongation of repolarization (as observed by an increased QT interval) alone is not sufficient to increase the risk of proarrhythmia, specifically in this case torsades de pointes. However, risk for torsades is increased when QT prolongation is accompanied by an increase in early after-depolarizations (EADs) and increased dispersion of repolarization (Figure 1). The risk of EADs increases as the action potential duration increases. EADs can produce ectopic beats and extrasystoles, serving as the trigger to initiate and then perpetuate torsades de pointes. Dispersion of repolarization refers to the spatial variability among different parts of the ventricular wall (i.e., the endocardium, midmyocardium, and epicardium) in the time to repolarization (i.e., refractoriness). The dispersion is the difference between the longest action potential duration and the shortest action potential duration in different areas. An increase in the dispersion of repolarization can be viewed at the necessary substrate for proarrhythmia, setting the stage for reentry (i.e., abnormal cardiac impulse conduction). Certain class III antiarrhythmic agents associated with an increased incidence of torsades de pointes increase the action potential duration in all parts of the ventricular wall, but they increase it to a much greater extent in the midmyocardium, thereby increasing the dispersion of repolarization. Since QT prolongation must be accompanied by an increase in EADs, as well as an increase in the dispersion of repolarization throughout the myocardium, a more thorough assessment of the electrophysiologic effects of ranolazine is needed to predict the risk of proarrhythmia.

Animal work has demonstrated that ranolazine prolongs the action potential duration and the QT interval, but it suppresses EADs and reduces dispersion of repolarization. In addition, it was noted that ranolazine suppresses the proarhythmic effects of some drugs that prolong the QT interval (e.g., d-sotalol). Overall, it appears that the electrophysiologic effects of ranolazine are similar to those of amiodarone, which is associated with a very low incidence of proarrhythmia and torsades de pointes.

Because the cellular electrophysiology underlying the effect of ranolazine on the QT interval is fundamentally different from that of drugs known to cause torsades de pointes, ranolazine is not expected to cause torsades de pointes. To date, no cases have been reported in clinical trials with ranolazine. However, adequate postmarketing surveillance will likely be necessary to adequately define the proarrhythmic potential of the agent.

**Place in Therapy**

Ranolazine therapy appears to be useful as add-on therapy in patients with extensive CAD and angina that is not controlled with conventional antianginal agents. Ranolazine may be particularly beneficial for the subset of patients who are not candidates for revascularization and remain symptomatic despite the use of maximum dosages of multiple antianginal agents, or have hemodynamic limitations that preclude initiation or titration to optimal dosages of conventional antianginal agents. As with all drug therapies, the risks associated with ranolazine use (e.g., potential for drug interactions) need to be considered before initiating therapy.

Additional clinical experience will help clarify the place in therapy for ranolazine. The long-term efficacy and safety of ranolazine treatment for up to 12 months will be evaluated in approximately 5,500 patients with non-ST elevation acute coronary syndromes treated with standard therapy in the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndromes study (also referred to as MERLIN-TIMI 36). This phase 3, international, randomized, double-blind, placebo-controlled, parallel-group study began in October 2004. The primary end point is the time to first occurrence of any element of the composite of cardiovascular death, MI, or recurrent ischemia. Additional end points include exercise tolerance test performance, quality of life, and pharmacoeconomic benefit.

**Conclusion**

Ranolazine has a unique mechanism of action that may be complementary to that of conventional antianginal agents. Ranolazine, when added to conventional antianginal therapy, is effective for the treatment of chronic angina. Ongoing studies will better define the effect of ranolazine on hard outcomes such as mortality, as well as its place in therapy in the treatment of patients throughout the spectrum of CAD. Despite the drug’s proven benefit, providers will need to be familiar with the potential for drug interactions, disease interactions, and defined contraindications.
tions in order to use the medication in the safest manner possible. Although ranolazine can prolong the QT interval, it is not expected to cause proarrhythmia because of its overall electrophysiologic effects.

DISCLOSURES
This article is based on a presentation given by the author at a symposium entitled “Emerging Therapies for Management of Patients with Stable Angina: Focus on Clinical Efficacy and Outcomes” at the Academy of Managed Care Pharmacy’s 18th Annual Meeting and Showcase in Seattle, Washington, on April 5, 2006. The symposium was supported through an educational grant from CV Therapeutics, Inc. The author received an honorarium from CV Therapeutics, Inc. for participation in the symposium. He has served as a consultant for CV Therapeutics, Inc.

REFERENCES