Ranolazine extended-release for chronic angina

Chronic angina continues to plague many of our patients, despite revascularization attempts and/or evidence-based medical therapy. Approved in the USA for patients with ischemic heart disease and chronic angina in January 2006, ranolazine extended-release is the latest addition to the armamentarium of anti-anginal medications. Although the exact mechanism of action to reduce angina and ischemia remains unclear, ranolazine appears to influence sodium–calcium homeostasis, and has proven effective in delaying and/or reducing ischemia in patients with angina. This unique medication has a favorable side-effect profile, with negligible impact on heart rate and blood pressure, in addition to potential antiarrhythmic and antidiabetic actions. This article will review the indications, contraindications and data supporting use of ranolazine in patients with chronic angina.

KEYWORDS: angina, angina pectoris, anti-anginal, ischemia, ranolazine

Laura M Gruen[†] & Carl J Pepine

[†]Author for correspondence: Division of Cardiovascular Medicine, University of Florida College of Medicine, 1600 SW Archer Road/ Box 100277, Gainesville, FL 32610-0277, USA Tel.: +1 352 846 0620; Fax: +1 352 846 0314; gruenlm@medicine.ufl.edu

Coronary heart disease affects over 15 million people in the USA, and approximately 9 million have angina pectoris [101]. However, this likely represents only the 'tip of the iceberg' of symptomatic chronic coronary disease syndromes (CCS), considering difficulties with recognition of chest symptoms and access to medical care capable of making an appropriate diagnosis. In Americans aged 40–74 years, the prevalence of angina pectoris is higher in women than men [101]. Despite advances in prevention, as well as invasive and noninvasive management, millions of patients have limited their lifestyles to avoid angina episodes. As our aging population continues to increase in size, death rates for acute coronary syndrome (ACS) continue to decrease [101], and as risk conditions such as obesity, metabolic syndrome, diabetes and hypertension become more prevalent, the number of patients with chronic angina will continue to grow.

Overview of the market

Traditionally, three major classes of medications have been employed to treat patients with chronic angina: calcium antagonists, β-adrenergic blockers, and long-acting nitrates (Table 1). All of these classes of drugs prevent or delay angina by limiting increases in myocardial oxygen demand to permit prolonged activity before ischemia occurs. Only β-blockers have reduced long-term mortality, but this benefit is documented only in postmyocardial infarction and heart failure patients [1,2]. The standard approach to treatment of angina is a combination of two or three of the preceding classes of drugs titrated to control symptoms while minimizing side effects. Although these medications have proven effective in delaying the onset of ischemia and angina in randomized trials, many patients continue to have lifestyle-limiting angina, despite maximum tolerated doses of these medications. Coronary revascularization (by percutaneous intervention and/or bypass surgery) is usually offered at some point in the care of these patients, but most continue to use some antianginal drug(s) even after successful revascularization procedures. When angina continues and revascularization attempts have been exhausted owing to comorbidities or lack of conduits or target vessels (usually diffuse disease), few proven alternative strategies have been available. They include enhanced external counterpulsation (EECP), transmyocardial revascularization (TMR), spinal cord stimulation or even evaluation for cardiac transplantation. Each of these procedures has important limitations. Thus, for most chronic angina patients, medical therapy continues to be the primary method for treatment.

In many patients, the clinician is limited in the deployment of maximal doses of multiple drugs by the patient's heart rate and/or blood pressure, or other side effects such as fatigue, sexual dysfunction, depression or bronchospasm. Both nondihydropyridine calcium antagonists (verapamil and diltiazem) and β-blockers decrease heart rate. All calcium antagonists, β-blockers and nitrates reduce blood pressure. For angina patients with reduced ejection fraction and/or heart failure from prior myocardial infarction,

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Table 1. Comparison of ranolaszine to traditional antianginals.

	Hemodynamic effects	Conduction system effects	Other effects
Ranolazine	No significant effects	Possible prolonged QTc	Decrease in HbA1c
Calcium antagonists	Lower blood pressure; negative inotropic (varies within class)	Slowed SA and AV node conduction; dihydropyridines may cause reflex tachycardia	Verapamil can inhibit insulin release at high doses; may interfere with *in vitro* platelet aggregation
β-blockers	Lower blood pressure; negative inotropic	Slowed AV node conduction	Inhibition of lipolysis and glycogenolysis; increases in VLDL and decreased HDL
Long-acting nitrates	Lower blood pressure; decreased preload and decreased cardiac output; vasodilation of coronary arteries	Possible reflex tachycardia	Decreases platelet aggregation

AV: Atrioventricular; HDL: High-density lipoprotein; SA: Sinoatrial; VLDL: Very-low-density lipoprotein.

calcium antagonists such as diltiazem and verapamil are not recommended [102]. This is due to negative inotropic effects with the potential to exacerbate heart-failure-related symptoms. Clearly, a novel agent that would decrease angina episodes without affecting heart rate or blood pressure or exacerbating heart failure, would be highly desirable for the many patients plagued with chronic stable angina.

Introduction to ranolazine extended-release

Sustained-release ranolazine was approved by the US FDA on January 27, 2006, for use in patients with chronic stable angina who are unresponsive to traditional anti-anginal medications such as β-blockers, calcium channel blockers and long-acting nitrates. Currently, ranolazine is not approved for use in patients with acute episodes of angina, ACS or unstable angina.

Chemistry

Ranolazine ([(+)N-(2,6-dimethylphenyl)-4(2-hydroxy-3-(2-methoxyphenoxy)-propyl)-1-piperazine acetamide dihydrochloride]) is a piperazine derivative marketed as Ranexa® by CV Therapeutics Inc. (CA, USA) (Figure 1).

Pharmacodynamics

The exact mechanism of action of ranolazine in chronic angina is not yet completely understood. Ranolazine had been shown to inhibit myocardial fatty acid oxidation [3], which in turn should increase glucose oxidation, which is a more oxygen and energy-efficient pathway for the cardiac myocytes. However, evidence suggests that this effect requires very high plasma concentrations of the drug and only contributes minimally [4,5], if at all, to the anti-ischemic and anti-angina effect documented with plasma concentrations achieved in trials. Alternatively, ranolazine appears to influence cardiomyocyte sodium–calcium homeostasis. It inhibits the I_{kr}, late I_{na} and late I_{ca} channels, particularly the late I_{na} channels [7]. The late I_{na} channels allow Na^+ influx, which can increase action potential duration, thus leading to arrhythmias and to intracellular Ca^{2+} overload, which has the potential to impair diastolic and systolic function [5]. In a normally functioning heart, the late I_{na} channels play a small role in action potential generation, but this contribution is amplified in the ischemic or hypoxic heart. Therefore, by inhibiting late I_{na} channels in ischemic or failing hearts, ranolazine may have some cardioprotective effects [5]. However, how this action contributes to an effect that favorably shifts the myocardial oxygen demand–supply balance in CCS patients to permit longer exercise duration before the ischemia threshold is reached is unclear.

Pharmacokinetics & metabolism

The peak plasma concentration of ranolazine extended-release (ER) occurs 2–5 h after ingestion, and it has a half-life of 7 h. Twice-daily dosing achieves steady state plasma levels at approximately 3 days [6]. Ranolazine undergoes hepatic metabolism to at least 11 different metabolites, the majority through the CYP3A4 pathway. In total, 10–15% of the compound is metabolized through the CYP2D6 pathway. The drug is ultimately excreted by the kidneys. Variables such as age, severity of heart failure, gender and presence or absence or diabetes mellitus did not appear to affect the pharmacokinetics of ranolazine-ER significantly. However, levels of the drug are significantly elevated in patients with mild, moderate or severe hepatic impairment, and its use is therefore currently contraindicated in patients with clinically significant hepatic dysfunction

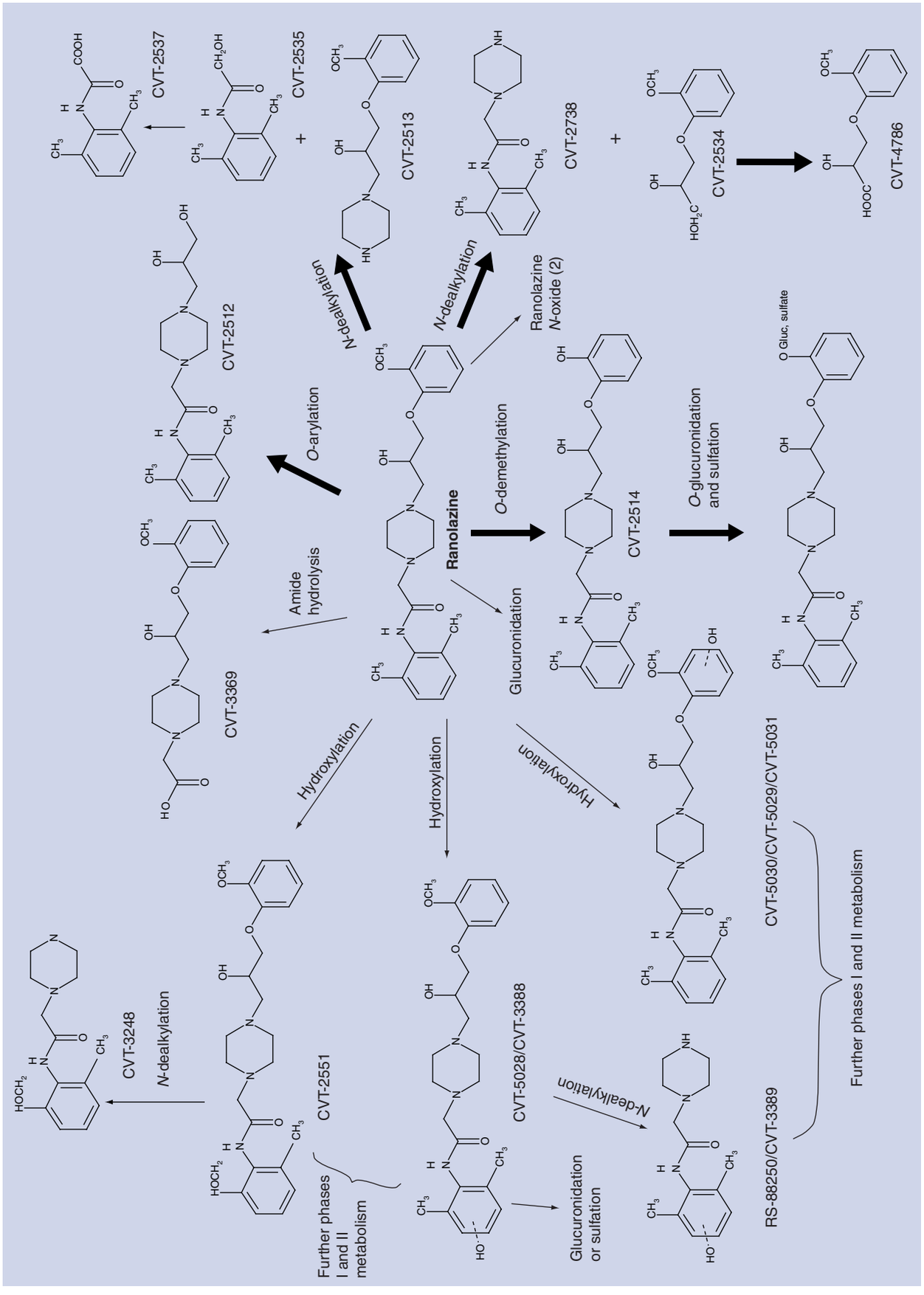

Figure 1. Chemical structure and metabolism of ranolazine. Reproduced with permission from [16].

[6]. Ranolazine has not been evaluated in patients with end-stage renal disease on hemodialysis, but levels can be elevated up to 50% in patients with renal impairment [6]. When tested in several patients with severe renal dysfunction, ranolazine caused an elevation of mean diastolic blood pressure of 10–15 mmHg [8].

Clinical efficacy

Phase III studies

Immediate-release ranolazine was initially evaluated in several controlled trials (TABLE 2), and two are summarized below since they provide the background and justification for studies with the newer ER preparation currently marketed.

The efficacy and safety of immediate-release ranolazine was assessed during a randomized, double-blind, placebo-controlled crossover study [7]. In the qualifying phase, at least one anti-anginal drug was withdrawn from the regimen of 312 patients with chronic stable angina while they took placebo. After exercise time had shortened by 1.0 min or more, patients were randomly assigned either immediate-release ranolazine in three dosing regimens (267 mg three-times daily, 400 mg twice daily or 400 mg three-times daily) or placebo. After each week of treatment, exercise tolerance and ranolazine plasma concentrations were measured. All exercise parameters significantly ($p \leq 0.02$) improved with ranolazine (all regimens combined) at peak plasma concentrations (range: 1.576–2.492 ng/ml) compared with placebo, without differences in rate–pressure product (RPP). Although similar trends persisted at trough plasma concentrations (275–602 ng/ml), only time to ischemic ST-segment depression remained statistically significantly prolonged. The conclusion was that immediate-release ranolazine is effective and well tolerated, but either larger or more frequent doses or an ER formulation would be required for clinical use.

In another trial, immediate-release ranolazine (400 mg three-times daily), atenolol (100 mg once daily) and placebo for 7–10 days each were compared using a three-period crossover design [8]. While both atenolol and ranolazine treatments significantly delayed times to angina and ST segment depression compared with placebo, when atenolol was compared with ranolazine, the differences in times to angina and ST segment depression were not statistically significant. However, total exercise time was prolonged with ranolazine compared with atenolol (mean difference 21.1 s; $p < 0.05$). With atenolol, RPP decreased (a reflection of decreases in heart rate and blood pressure), but with ranolazine, no decreases in RPP were observed, despite effective anti-anginal and anti-ischemic effects.

The above positive experiences led to development of the ER formulation, which was then tested in four recent trials. In the Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) trial, patients with exertional angina on β-blockers, calcium antagonists and/or nitrates were randomized to receive ranolazine-ER (500, 1000, 1500 mg twice daily) or placebo [9]. Except for short-acting nitrates, other anti-anginal medications were discontinued. Compared with placebo, patients in all three ranolazine ER dose groups had increased exercise time, time to angina and time to 1 mm of ST segment depression. Exercise time increased by 94 s in the 500-mg dose group, by 103 s in the 1000-mg dose group, and by 116 s in the 1500-mg dose group, compared with an increase of 70 s in the placebo group. However, side effects at 1500 mg were greater than any other dose, and this dose is not currently approved, nor is it being investigated further.

The Combination Assessment of Ranolazine In Stable Angina (CARISA) trial evaluated ranolazine ER as an adjunct to another low-dose anti-anginal agent in 823 stable angina patients, despite standard anti-anginal medications and revascularization in a randomized, double-blind, placebo-controlled design [10]. Patients were maintained on amlodipine 5 mg, atenolol 50 mg or diltiazem 180 mg, and were then randomized to receive ranolazine 750 mg twice daily, ranolazine 1000 mg twice daily or placebo for 12 weeks. Treadmill exercise duration increased by 115.6 s from baseline with ranolazine, compared with a corresponding increase of 91.7 s with placebo. The ranolazine ER groups also experienced increased time-to-angina and time-to-onset of ischemic ST-segment depression during exercise testing, as frequency of angina and nitroglycerin use declined.

In the Efficacy of Ranolazine in Chronic Angina (ERICA) trial, 558 patients with chronic stable angina despite amlodipine 10 mg/day were randomized to receive ranolazine ER 1000 mg or placebo twice daily for 6 weeks [11]. Patients taking other anti-anginal medications were excluded. Patients were assessed by self-reported nitroglycerin consumption and angina frequency logs, as well as the Seattle Angina Questionnaire (SAQ). Patients in the ranolazine-ER group experienced 25% less nitroglycerin tablet use per week and 0.43 fewer episodes of angina per week after 6 weeks of treatment. Subgroup analysis showed that patients with greater than 4.5

Table 2. Summary of Phase III clinical trials.

	Study design (n)	Treatment	Primary outcome measures	Secondary outcome measures	Summary of study results	Ref.
Ranolozine Study Group (*Am. J. Cardiol.* 1999)	Randomized, double-blind, placebo-controlled crossover study (312)	IR ranolazine 267 mg t.i.d., 400 mg b.i.d., and 400 mg t.i.d. or placebo for 1 week and again during a 5th 1-week period	Exercise duration	Time to onset angina and time to 1 mm ST depression and plasma peak and trough ranolazine levels	IR ranolazine effective anti-ischemia and antianginal agent at peak, but not at trough plasma levels; therefore, a sustained or extended release preparation would be required for clinical use	[7]
RAN080 (*Am. J. Cardiol.* 2005)	Randomized, double-blind, placebo-controlled, three-period crossover study (158)	IR ranolazine 400 mg t.i.d., atenolol 100 mg, or placebo for 1 week each. β-blockers withdrawn prior to start of study	Time to onset of angina	Time to 1 mm ST depression, total exercise duration	Total exercise duration increased more with IR ranolazine compared with atenolol or placebo. Atenolol and IR ranolazine yielded similar improvements in time to angina and time to ST depression	[8]
MARISA (*J. Am. Coll. Cardiol.* 2004)	Randomized, placebo-controlled, double-blind, four period crossover study (191)	Ranolazine ER 500, 1000 or 1500 mg, or placebo dosed b.i.d. for 1 week each; other anti-anginals discontinued	Exercise duration	Time to angina and time to 1 mm ST depression	Ranolazine ER, monotherapy increased exercise duration, time to angina and time to ischemic ST depression	[9]
CARISA (*JAMA* 2004)	Randomized, placebo-controlled, double-blind, three-group parallel trial (823)	Ranolazine ER 750 or 1000 mg, or placebo b.i.d. in addition to atenolol, diltiazem or amlodipine	Exercise duration	Time to angina, angina attacks, nitroglycerin use, time to 1 mm ST depression	Ranolazine ER in combination with standard therapy, increased exercise duration, time to angina, and time to ST depression compared with standard therapy alone	[10]
ERICA (*J. Am. Coll. Cardiol.* 2006)	Randomized, placebo-controlled, double-blind (565)	Ranolazine ER 1000 mg b.i.d. or placebo for 6 weeks following a 500 mg b.i.d. 1 week initial phase; in addition to amlodipine 10 mg/day	Frequency of angina attacks	Nitroglycerin consumption and change from baseline in five dimensions of SAQ	Ranolazine ER, in combination with amlodipine, reduced the frequency of angina episodes and NTG consumption when compared with amlodipine alone	[11]
MERLIN (*JAMA* 2007)	Randomized, double-blind, placebo-controlled, parallel group trial (6560)	Intavenous ranolazine infusion over 12–96 h followed by ranolazine ER b.i.d. orally	Time to first occurrence of any element of the composite of CV death, MI, recurrent ischemia	Ischemia on ECG monitoring, hospitalization for new or worsening CHF, QoL measures, exercise performance	Ranolazine not effective in reducing death or MI in ACS, when added to standard therapy. However, it reduced recurrent ischemia, arrhythmias and HbA1c and improved exercise performance during 1 year follow-up	[12]

ACS: Acute coronary syndrome; b.i.d.: Twice daily; CHF: Congestive heart failure; CV: Cardiovascular; ER: Extended release; IR: Immediate release; MI: Myocardial infarction; NTG: Nitroglycerin; SAQ: Seattle Angina Questionnaire; t.i.d.: Three-times daily; QoL: Quality of life.

episodes of angina per week had statistically significant less episodes of angina, nitroglycerin use and SAQ angina frequency. Patients with fewer than 4.5 episodes of angina per week showed only reduction in angina frequency.

The Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndromes (MERLIN-TIMI36) trial examined safety and efficacy of ranolazine in patients with non-ST elevation MI [12]. A total of 6560 ACS patients considered moderate to high risk for death or recurrent ischemic events were randomized to ranolazine or placebo. Ranolazine was initiated as a 200 mg intravenous bolus dose, and then continued as an infusion for 12–96 h followed by oral dosing of the ER preparation 1000 mg twice daily. Median follow-up was 348 days. Primary outcome was the first occurrence of any of the following: cardiovascular death, myocardial infarction or recurrent ischemia. Safety outcomes included arrhythmias, death or cardiovascular hospitalization. There was no statistically significant difference between ranolazine and placebo for the primary outcome or myocardial infarction, cardiovascular death considered separately, or the composite of the two. However, ranolazine significantly decreased recurrent ischemia compared with placebo, (430 [13.9%] vs 494 [16.1%]). No appreciable differences in safety measures between placebo and ranolazine were detected, but importantly, ranolazine significantly reduced arrhythmias assessed by continuous electrocardiogram monitoring in the first week after admission. It appears effective for both atrial and ventricular arrhythmias occurring during the initial week after presentation with ACS [13].

In subgroup analysis of 1737 patients with chronic angina treated with ranolazine ER prior to MERLIN, there was a suggestion of gender difference in efficacy. Ranolazine yielded similar efficacy in both genders with regard to decreased angina frequency and less nitroglycerin use; however, women appeared to show less increase in exercise tolerance than men. Reasons for this discrepancy were unclear, but likely multifactorial, including selection bias. Importantly, none of the studies were adequately powered to delineate gender-specific efficacy differences. In all four of the major studies prior to MERLIN, women comprised 28% or less of each of the study populations [8–11]. However, in MERLIN 2291 women were included, and they had an overall beneficial effect with ranolazine for reduction of the primary outcome (hazard ratio [HR] = 0.83; 95% confidence interval [CI]: 0.70–0.99). This result was driven by a 29% reduction in recurrent ischemia (p = 0.002) [12]. Based on the current body of evidence, it appears that ranolazine is more effective in women than in men.

The efficacy and safety of ranolazine compared with placebo in the subgroup of patients with any history of prior angina (n = 3565) followed for approximately 1 year in the MERLIN trial was recently presented [14,15]. Patients with prior angina received evidence-based therapy (with 95% using aspirin, 77% statins, 89% β-blockers and an average of 2.7 anti-anginal drugs) balanced between the two treatment groups. Among these patients with prior angina, the primary outcome (cardiovascular death, myocardial infarction or recurrent ischemia) occurred in 29.4 versus 25.2% (placebo vs ranolazine; HR: 0.86; 95% CI: 0.75–0.97; p = 0.017). Cardiovascular death or myocardial infarction did not differ between treatment groups. However, ranolazine significantly reduced risk of recurrent ischemia (HR: 0.78; p = 0.0021), worsening angina (HR: 0.76; p = 0.0482) and intensification of anti-anginal therapy (HR: 0.78; p = 0.0093). Exercise duration at 8 months was 482 s in placebo-treated patients versus 514 s (p = 0.002) among ranolazine-treated patients. All-cause mortality and symptomatic arrhythmias did not differ between ranolazine- versus placebo-treated groups. The authors concluded that in the largest study of ranolazine thus far (subgroup of patients with prior angina and established coronary artery disease), ranolazine was effective in reducing angina and recurrent ischemia in a substantially broader group of patients than previously studied.

The safety and efficacy of ranolazine is similar in diabetic and nondiabetic patients. Interestingly, *post hoc* analysis of the CARISA trial participants enrolled in an open-label extension for 12 weeks demonstrated that ranolazine ER improved glycemic control in diabetic patients. Diabetic patients receiving ranolazine 750 mg twice daily had decreases in HbA1c values of 0.48% (p = 0.008) compared with diabetics receiving placebo. Likewise, patients receiving 1000 mg twice daily had decreases of 0.70% (p = 0.0002) compared with diabetic patients in the control group. Stratification based on insulin use showed even greater reductions in HbA1c values in diabetics treated with insulin compared with those using only oral antidiabetic medications. This suggestion was confirmed prospectively in MERLIN,

which included 2220 diabetic patients [14]. Among the 4306 patients (diabetic and nondiabetic) with serial data, ranolazine-ER significantly reduced HbA1c at 4 months (change from baseline: -0.30%) compared with placebo (-0.04%; p = 0.001). Among those with diabetes, HbA1c declined from 7.5 to 6.8% (change: -0.64%; p < 0.001). Patients with diabetes were significantly more likely to achieve HbA1c less than 7.0%, a marker of good glycemic control, when treated with ranolazine ER when compared with placebo (59 vs 49%; p < 0.001). In addition, worsening hyperglycemia at 1 year was less likely in those treated with ranolazine ER (14.25 vs 20.65; HR: 0.063; 95% CI: 0.51–0.77; p < 0.001). Finally, in those without diabetes at baseline, the incidence of new fasting glucose greater than 110 mg/dl or HbA1c of 6.0% or greater was also reduced with ranolazine ER (31.8 vs 41.2%; HR: 0.68; 95% CI: 0.53–0.88; p = 0.003) [14]. These data may indicate that ranolazine has an important effect on insulin sensitivity, and it did not appear to affect fasting serum lipid levels.

Postmarketing surveillance

The reports of the MERLIN trial, which studied patients with acute coronary syndrome (summarized above), represent postmarketing data. No additional data were available for this report.

Safety & tolerability

Potential side effects of ranolazine include constipation, asthenia, nausea, dizziness, palpitations, tinnitus, peripheral edema, abdominal pain and headache [6], yet it was well tolerated by study patients in general. In long-term follow-up, abrupt cessation of ranolazine did not appear to cause rebound angina. The usual starting dose is 500 mg twice daily. If this is ineffective, titration to 1000 mg twice daily is the maximal recommended dose. Side effects were more pronounced at doses at or above 1500 mg twice daily in clinical trials.

Any medication that induces CYP3A4 should not be used with ranolazine. Similarly, ranolazine should not be used with strong CYP3A4 inhibitors. However, moderate inhibitors of CYP3A4, such as diltiazem or verapamil, can be given with ranolazine, but the dose of ranolazine should be limited to 500 mg twice daily.

Other medications frequently taken by cardiac patients include simvastatin and digoxin, the levels of which may be elevated by ranolazine through its inhibition of metabolic pathway for these drugs. The concomitant use of digoxin is not contraindicated, but dosage adjustment may be required. Lower doses of ranolazine may also be needed when used in combination with drugs transported by P-glycoproteins. Ranolazine does not appear to interact with warfarin in clinical studies.

Ranolazine caused a dose-dependent QTc prolongation in clinical trials. In the CARISA trial, the average increase in QTc duration in patients taking 1000 mg twice daily was 9.2 ms. Patients with moderate or severe hepatic dysfunction exhibited even further QTc prolongation. One case of torsades de pointes was reported in the treatment group in the MERLIN trial. Interestingly, one case was reported in the placebo group as well. Nevertheless, QTc intervals must be monitored in patients taking this drug. It is currently recommended that an electrocardiogram be obtained at baseline and at follow-up intervals, particularly after steady-state is reached, in patients receiving ranolazine. There is no current recommendation for inpatient monitoring while patients initiate therapy. Ranolazine should be avoided altogether in patients with prolonged QTc at baseline, or those who are taking medications known to prolong the QT interval (see TABLE 1 for comparison of ranolazine to nitrates, β-blockers and calcium-channel blockers).

Regulatory affairs

Ranolazine is currently only approved for use in the USA for the treatment of chronic angina. Ranolazine has recently been approved by the central European Regulatory Agency (EMEA).

Conclusion

The Phase III trial data available support the usefulness of ranolazine ER as an anti-anginal agent for patients with chronic angina. Administration of ranolazine ER, either as monotherapy or in addition to other anti-anginal agents, provides increased exercise time, increased time to angina, and decreased use of nitroglycerin. Unlike other standard anti-anginal agents, these effects were seen without appreciable decreases in heart rate or blood pressure. Other side effects observed in clinical trials were generally mild and tolerable if doses were kept to a maximum of 1000 mg twice daily.

Short-acting ranolazine was shown to be equivalent to atenolol in reducing frequency of angina episodes, and superior to atenolol in improving exercise time without the usual β-blocker side effects. To date, this is the only study that has compared ranolazine directly with

Executive summary

- Ranolazine is currently approved for patients with chronic stable angina.
- The dosing regimen is 500–1000 mg twice daily.
- Ranolazine has a negligible impact on heart rate and blood pressure, and is otherwise very well tolerated.
- The mechanism of action is novel, as ranolazine has effects on sodium–calcium homeostasis, but the anti-ischemia mechanism is not completely understood.
- It should not be used in patients with hepatic impairment or those taking medications that inhibit the cytochrome P450 system.
- Current labeling recommends patients should be monitored for QTc prolongation while on ranolazine.
- Ranolazine has potentially important antiarrhythmic and antidiabetic effects.

a standard anti-anginal medication. No study has yet compared ranolazine ER to a standard anti-anginal medication.

Ranolazine is currently approved for the treatment of chronic angina. Owing to the potential for QTc prolongation, the current labeling recommends close monitoring of the QTc interval during therapy. In addition, many medications interact with ranolazine and cannot be used in conjunction.

Expert commentary

The data to support the efficacy of ranolazine are strong, and clearly document that it is an effective anti-anginal, as monotherapy or in combination with other standard treatment medications. Its relative lack of hemodynamic consequences is attractive, particularly in patients prone to lower blood pressure and heart rate-related symptoms from other necessary medications. The effect of ranolazine on QTc intervals now appears to have been clarified, as it has anti-arrhythmic effects without proarrhythmic effects.

No single study has yet to overwhelmingly show that ranolazine is superior to any current anti-anginal agent, and clinicians should not hastily exchange their patient's anti-anginal regimen for ranolazine based on the current data. However, ranolazine is an ideal medication for the many patients with chronic, stable angina, who are already on maximum doses of β-blockers, long-acting nitrates, and often calcium antagonists as well. If these patients are still experiencing life-interfering angina, ranolazine should be added in attempt to control their symptoms (so long as there are no contraindications).

Particularly interesting, and a topic of future research, is the potential anti-arrhythmic effect of ranolazine. As determined after data analysis from the MERLIN study, ranolazine tended to reduce arrhythmias in patients with ACS in the period just after randomization to the ranolazine arm. Despite its effect on QTc prolongation, a side effect common to anti-arrhythmic medications affecting the same ion channels, ranolazine may find a niche in the future as an effective anti-arrhythmic medication, particularly given its lack of important hemodynamic effects. Perhaps ranolazine will also prove to have beneficial effects in diastolic heart failure, and in other cardiomyopathies via its action on cardiomyocyte sodium–calcium homeostasis.

Clinical trial data supports a reduction in glycosylated hemoglobin levels in diabetic patients, with a more profound effect in those treated with insulin. As the obesity rate and number of patients with metabolic syndrome soar, this effect may prove to be another very useful 'unpredicted' effect of this medication designed to treat angina.

Future perspective

In 5 years, we believe that this agent, or one of its more active metabolites, will be the initial anti-anginal/anti-ischemic agent of choice for CCS patients with continuing angina. It is also likely that it will have some antiarrhythmic indications, and perhaps indications for some forms of heart failure. Other metabolites may appear to have potential as adjunctive drugs for diabetes management.

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▪▪ **Randomized, parallel group, double-blind, placebo-controlled trial of 823 patients with chronic angina randomly assigned to receive placebo or sustained-release ranolazine (750 or 1000 mg) twice-daily. Sustained-release ranolazine increased exercise capacity at trough plasma levels when added to conventional antianginal agents.**

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▪ **Patients (n = 565) with chronic angina despite amlodipine (10 mg/day) were randomized to 1000 mg sustained-release ranolazine or placebo twice daily for 6 weeks. Ranolazine reduced angina frequency and nitroglycerin consumption compared with placebo and was well tolerated.**

12 Morrow DA, Scirica BM, Karwatowska-Prokopczuk E *et al.*; MERLIN-TIMI 36 Trial Investigators: Effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes: the MERLIN-TIMI 36 randomized trial. *JAMA* 297, 1775–1783 (2007).

▪▪ **Moderate- to high-risk ACS patients (n = 6560) were randomized to placebo or ranolazine. There was no significant difference between ranolazine and placebo for the primary outcome (first occurrence of cardiovascular death, myocardial infarction or recurrent ischemia), but recurrent ischemia decreased with ranolazine (430 [13.9%] vs 494 [16.1%]).**

13 Scirica BM, Morrow DA, Hod H *et al.*: Effect of ranolazine, an antianginal agent with novel electrophysiological properties, on the incidence of arrhythmias in patients with non ST-segment elevation acute coronary syndrome: results from the Metabolic Efficiency with Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) randomized controlled trial. *Circulation* 116, 1647–1652 (2007).

▪▪ **Ranolazine decreased both atrial and ventricular arrhythmias in acute coronary syndrome (ACS) patients.**

14 Morrow DA, Scirica BM, Chaitman BR et al.: Effect of ranolazine on hemoglobin A1c in the MERLIN-TIMI 36 randomized controlled trial. Circulation, 116, II539–II540 (2007) (Abstract #2453).

▪ **Ranolazine decreased HbA1c in acute coronary syndrome patients followed for approximately 1 year.**

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