

Ranolazine: New Paradigm for Management of Myocardial Ischemia, Myocardial Dysfunction, and Arrhythmias

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KEYWORDS

- Myocardial ischemia • Angina • Ranolazine • Heart failure
- Diastolic dysfunction

Anti-ischemia medications have traditionally focused on optimizing the determinants of the myocardial O₂ supply: demand balance. Because myocardial oxygen extraction is maximal at rest, the only way to improve the balance pharmacologically has been to reduce myocardial O₂ demand (ie, heart rate, blood pressure or afterload, myocardial contractility, or preload). The approved antianginal medications in the United States are effective by reducing one or more of these O₂ demand determinants (**Table 1**).

There are many patients, however, who have chronic coronary disease in whom this pharmacologic approach is inadequate. Many patients either cannot tolerate these conventional agents or have continuing symptoms of ischemia and angina despite their use.¹ Ranolazine, which was approved by the US Food and Drug Administration in January 2006, provides a mechanism of action to treat ischemia that has not hitherto been available. Ranolazine is effective to reduce manifestations of ischemia and angina, and it also holds potential promise to be effective in the management of left ventricular dysfunction, particularly diastolic dysfunction, and arrhythmias. This article provides an update on the available studies concerning the value of ranolazine across the spectrum of cardiovascular disease.

MECHANISM OF ACTION

Ranolazine was first believed to be effective by inhibiting free fatty acid metabolism,² but it was later appreciated that ranolazine exerted this effect only at serum levels that are much higher than those observed in therapeutic usage.³ The mechanism of action now seems to be related to inhibition of the late inward sodium channel (late I_{Na}),⁴ which pathologically remains open in a wide variety of adverse stimuli to the myocardium. Electrical activation of the cardiomyocytes leads to brief opening of the membrane sodium channel, through which sodium ions rapidly enter the cell, generating the rapid depolarization or upstroke of the action potential (**Fig. 1A**).⁴ In the normal setting, the inward sodium channels then inactivate rapidly and remain closed during the plateau phase of the action potential. Other ion channels open following electrical activation, including calcium channels, and the calcium ions that enter the cell during the plateau phase of the action potential then trigger the release of the large stores of calcium ions from the sarcoplasmic reticulum. This increased concentration of cytoplasmic calcium initiates the interaction between actin and myosin and enables the contraction process to occur (see **Fig. 1A**). Following the myocardial

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Table 1
Antianginal pharmacologic management

Determinant of O ₂ Demand	β-Blocker	Nitrates	Ca ⁺⁺ Blocker	
			Dihydropyridine	Verap/Dilt
Heart rate	↓↓	0	↑/↑↑	↓↓
Afterload (BP)	↓	↓	↓↓↓↓	↓↓
Preload	0	↓↓↓	0	0
Contractility	↓↓	↑	↑↑	↓↓
Determinant of O ₂ supply				
Vasomotor tone	↑	↓↓	↓↓↓↓	↓↓↓↓

Abbreviations: BP, blood pressure; verap/dilt, verapamil/diltiazem; 0, no effect.

contraction, calcium ions are actively taken up back into the sarcoplasmic reticulum again and myocardial relaxation occurs.

In the setting of a wide variety of myocardial insults, however, including myocardial ischemia, hypertrophy, and oxidative stress, the late sodium channels either fail to inactivate (ie, fail to close) or reopen, such that sodium ions continue to enter the cell (see Fig. 1B).^{4,5} This intracellular overload of sodium ions leads to several major contractility, metabolic, and electrophysiologic disturbances.⁶ The elevation of intracellular sodium concentration leads to an increased exchange of intracellular sodium for extracellular calcium through the Na⁺/Ca⁺⁺ exchanger mechanism, such that the initial sodium overload leads to a subsequent intracellular calcium overload. The increased cytosolic calcium from the calcium overload state leads to the continued exposure of the actin and myosin contractile elements to the calcium ions, leading to a tonic contracture (see Fig. 1B). In the intact heart, this increased diastolic stiffness

leads to an abnormal elevation in myocardial contractile work, oxygen consumption, and compression of the vascular space during diastole.^{4,7} Compression of the vascular space causes a reduction in myocardial blood flow, which further reduces myocardial O₂ supply. This deleterious positive feedback system is detrimental in that the presence of ischemia leads to further exacerbation of ischemia (Fig. 2).

Ranolazine reduces the late sodium influx in a concentration-, voltage-, and frequency-dependent manner.^{4,6,7} By preventing the most upstream deleterious consequence of myocardial cellular dysfunction (ie, the intracellular sodium overload), all of the downstream consequences of the sodium overload, and the subsequent calcium overload, are reduced or prevented. In animal models ranolazine thus facilitates diastolic relaxation, preserves myocardial blood flow during ischemia and reperfusion, reduces myocardial O₂ consumption, and restores electrical stability.^{4,6-8} In healthy nonischemic, nonfailing myocytes, in

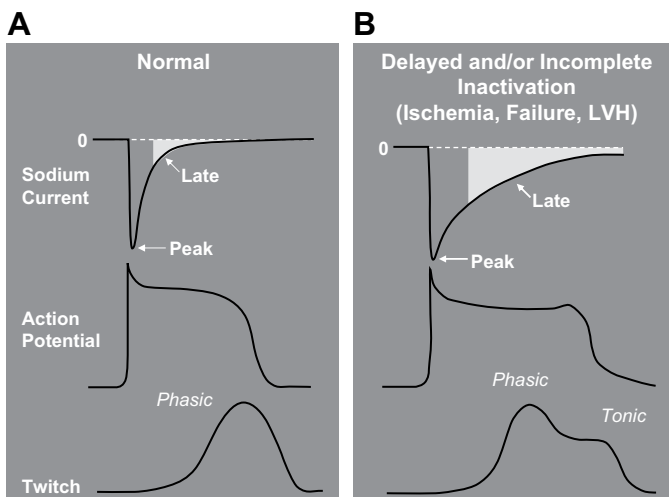


Fig. 1. Relation between late Na⁺ current and ventricular action potential and contraction. (A) Normal conditions. (B) Delayed or incomplete inactivation in the setting of ischemia, heart failure, or left ventricular hypertrophy (From Belardinelli L, Antzelevitch C, Fraser H. Inhibition of late (sustained/persistent) sodium current: a potential drug target to reduce intracellular sodium-dependent calcium overload and its detrimental effects on cardiomyocyte function. *Eur Heart J* 2004;6:14; with permission.)

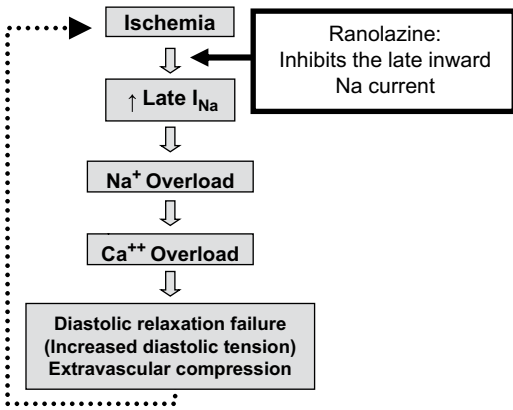


Fig. 2. Mechanism of action of ranolazine.

which the contribution of late I_{Na} is small, the drug does not have a measurable effect on cardiovascular performance at therapeutic plasma concentrations.⁹ The effect of ranolazine on late I_{Na} is more pronounced in ischemic or failing myocytes in which the current is amplified.⁹ Each of these pharmacologic effects may have important therapeutic application for patients who have cardiovascular disease, as discussed later.

PHARMACOKINETICS AND METABOLISM

Ranolazine is an active piperazine derivative available in oral and intravenous forms and is now manufactured in a sustained-release form.⁹ Its maximal plasma concentration is typically 4 to 6 hours after administration, and the average terminal elimination half-life is approximately 7 hours. The peak/trough difference is 1.6-fold with dosing of 500 to 100 mg twice a day.⁹ Ranolazine plasma concentrations that are therapeutically effective for chronic angina are in the range of 2 to 6 $\mu\text{mol/L}$.⁹ Oral bioavailability is in the range of 30% to 55%. Most of the metabolic biotransformation is through the cytochrome P450 3A4-mediated pathway,⁹ which is critical because

compounds such as ketoconazole, which inhibit the CYP3A isoenzymes, increase ranolazine levels in the range of 2.5 to 4.5 fold.⁹ Clearance of ranolazine is reduced by renal insufficiency and moderate hepatic impairment.⁹

Drug–drug interactions primarily are related to effects on the CYP3A metabolic pathway.⁹ Diltiazem, ketoconazole, verapamil, macrolide antibiotics, HIV protease inhibitors, and grapefruit juice inhibit the CYP3A enzyme system, and their concomitant use with ranolazine should be done with caution. Ranolazine also is a substrate and an inhibitor of P-glycoprotein. Verapamil, which inhibits P-glycoprotein, increases the absorption of ranolazine, with a consequent increase in plasma levels. Ranolazine increases digoxin levels.

THERAPEUTIC USES

Chronic Angina Pectoris

Conventional anti-ischemia medications reduce the development of ischemia primarily by reducing the determinants of myocardial O_2 demand: heart rate, blood pressure, preload, or contractility (Fig. 3). As myocardial ischemia develops intracellular calcium overload occurs, which leads to the consequences of ischemia, including systolic and diastolic myocardial dysfunction and electrical instability. Ranolazine has no clinically meaningful effects on the myocardial O_2 demand determinants, but exerts its anti-ischemic effect by preventing the calcium overload state and thereby reducing the subsequent myocardial stiffness that leads to reduced myocardial perfusion (see Fig. 3). A recent study demonstrated that the dose-related improvement in myocardial ischemia at submaximal and maximal exercise in patients who had stable coronary artery disease was attributable to an improvement in myocardial blood flow without meaningfully affecting heart rate or blood pressure.¹⁰ One can therefore anticipate that ranolazine would be an ideal complementary agent to

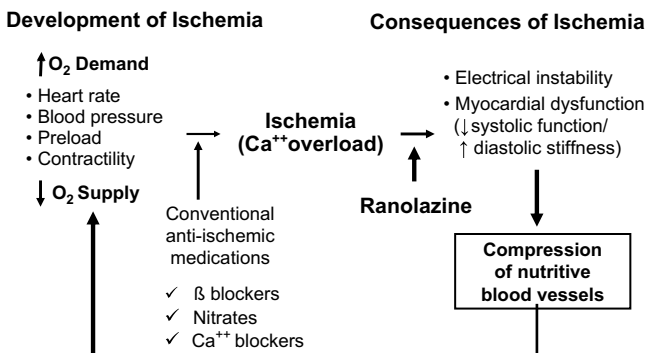


Fig. 3. Sites of action of anti-ischemia medication.

be used with medications that reduce the development of ischemia by reducing O_2 demand.

Monotherapy

The early studies of ranolazine in patients who had stable angina used the immediate-release formulation, whereas the more recent studies have used the sustained-release formulation. In comparison with placebo, ranolazine in the immediate-release formulation significantly reduced anginal episodes and nitroglycerin use, and significantly improved exercise duration and time to exercise-induced myocardial ischemia,¹¹ and was at least equally as effective as atenolol 100 mg every day (Fig. 4). The anti-ischemia effect of atenolol was attributable to its well-known reduction in the rate-pressure product at rest and during exercise, whereas the anti-ischemic effect of ranolazine occurred without any appreciable change in the determinants of myocardial O_2 demand (Fig. 5).¹¹

The Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) trial investigated the effect of the sustained-release formulation as single agent therapy of 500 mg twice a day, 1000 mg twice a day, or 1500 mg twice a day versus placebo twice a day in 191 patients who had chronic exertional angina with reproducible treadmill-induced myocardial ischemia and angina in a 4-week, double-blind, placebo-controlled crossover trial.¹² All three doses resulted in a significant, dose-dependent increase in exercise duration, exercise time to angina, and exercise time to 1-mm ST segment depression at trough and at peak drug effect compared with placebo

($P < .005$), although the incremental benefit was attenuated at dosages greater than 1000 mg twice a day.¹² The maximal increase in exercise duration compared with placebo was 56 seconds, whereas the maximal increase in time to angina or time to 1-mm ST-segment depression was 69 seconds (Fig. 6).

Combination regimens

The Combination Assessment of Ranolazine in Stable Angina (CARISA) trial was designed to evaluate the effect of the addition of ranolazine to a regimen of concomitant antianginal drugs, including atenolol (50 mg every day), diltiazem (180 mg every day), or amlodipine (5 mg every day).¹³ A total of 823 patients were studied in a parallel design, and ranolazine 750 mg or 1000 mg or placebo twice a day was administered in addition to the concomitant medications. Exercise tests were performed 2, 6, and 12 weeks after randomization. The addition of ranolazine was associated with a significant reduction in anginal frequency and nitroglycerin consumption, and an increase in exercise duration, time to angina, and time to 1-mm ST-segment depression compared with placebo both at trough and peak drug effect (Fig. 7). There was not a major difference between the ranolazine 750 mg and 1000 mg twice a day regimens. The increase in exercise duration of 115.6 seconds above baseline in both ranolazine groups versus 91.7 seconds in the placebo group ($P = .01$) did not depend on changes in blood pressure or heart rate, and this improvement in performance was sustained over the 12 weeks of therapy. The treatment-by-background interaction

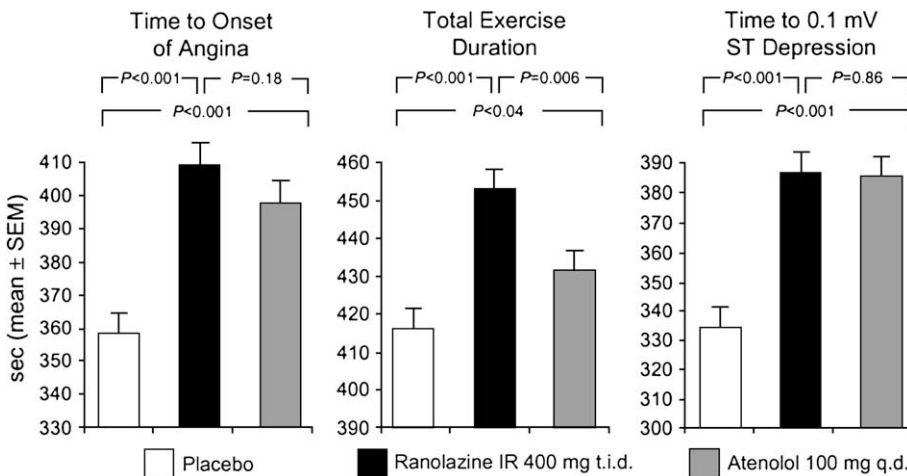


Fig. 4. Therapeutic effects of placebo ($n = 142$), ranolazine ($n = 142$), and atenolol ($n = 142$) on exercise tolerance and ischemic ST-segment depression in patients who have stable coronary disease. (From Rousseau MF, Pouleur H, Cocco G, et al. Comparative efficacy of ranolazine versus atenolol for chronic angina pectoris. *Am J Cardiol* 2005;95:313; with permission.)

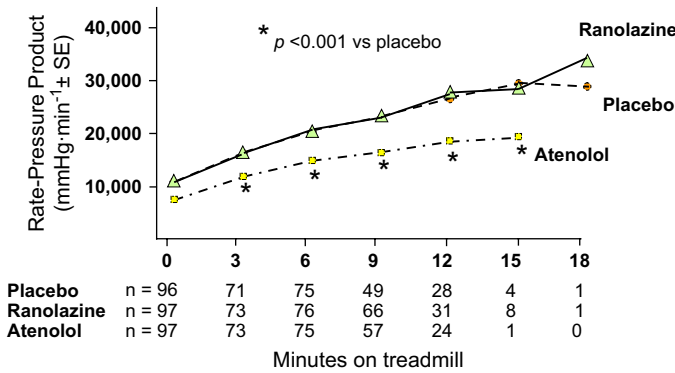


Fig. 5. Anti-ischemic effect of ranolazine without affecting heart rate or blood pressure at rest or during exercise. (From Rousseau MF, Pouleur H, Cocco G, et al. Comparative efficacy of ranolazine versus atenolol for chronic angina pectoris. *Am J Cardiol* 2005;95:314; with permission.)

term indicated no evidence of differential treatment effect according to background therapy received. Adverse events were reported in 26.4% of patients in the placebo group, 31.2% of patients in the ranolazine 750 mg group, and 32.7% of the ranolazine 1000 mg group. The most common dose-related adverse effects were constipation, dizziness, nausea, and asthenia, which occurred in less than 7% of the ranolazine-treated patients and less than 1% of the placebo-treated patients. There was a small, dose-related increase in the QTc interval of 6.1 and 9.2 milliseconds in the 750 mg and 1000 mg ranolazine groups, respectively, but there were no evident arrhythmias. Five patients taking 1000 mg ranolazine twice a day experienced syncope, but all were also taking an angiotensin-converting enzyme inhibitor and 4 of the 5 were also taking diltiazem, which is known to increase ranolazine levels. Although little or no effect of ranolazine was observed on blood pressure on 750 or 1000 mg twice a day dosages, postural hypotension and syncope have occurred in healthy volunteers given higher doses, up to 2000 mg twice a day, and this is believed likely because of α_1 -adrenergic receptor blocking activities at higher plasma concentrations.¹³ The patients in CARISA treated with

ranolazine who were diabetic experienced a significant reduction in hemoglobin A_{1c} compared with placebo (-0.70% , $P = .002$), although the mechanism of this improvement is not clear.

A more recent study investigated the antianginal effect of ranolazine versus placebo given to 565 patients who had persisting angina symptoms despite maximal dose amlodipine (10 mg every day) (Efficacy of Ranolazine in Chronic Angina [ERICA] trial).¹⁴ Compared with placebo, the addition of ranolazine 1000 mg twice a day was associated with a significant reduction in weekly anginal episodes and nitroglycerin consumption (to 3.31 episodes/wk on placebo versus to 2.88 episodes/wk on ranolazine, $P = .028$).¹⁴ There was a consistent treatment effect of ranolazine across the subgroups analyzed, including those also on long-acting nitrates versus those not on long-acting nitrates, men versus women, and patients aged less than 65 years versus those older than 65 years. An interesting subgroup analysis dividing patients on the basis of being above or below the median of weekly anginal frequency (4.5 episodes) indicated that those patients who had more frequent angina per week had a much more marked beneficial response to the addition of ranolazine, compared with those patients who had less frequent angina,

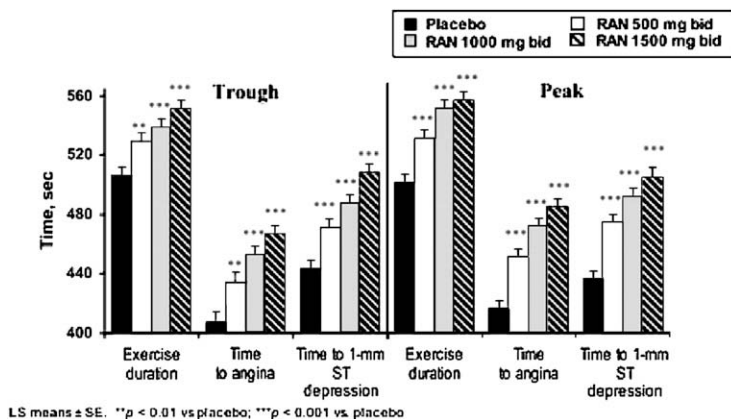


Fig. 6. Monotherapy with ranolazine increases exercise performance at trough and peak pharmacologic effect: the MARISA trial. (From Chaitman BR, Skettino SL, Parker JO, et al. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. *Modified from J Am Coll Cardiol* 2004;43:1378; with permission.)

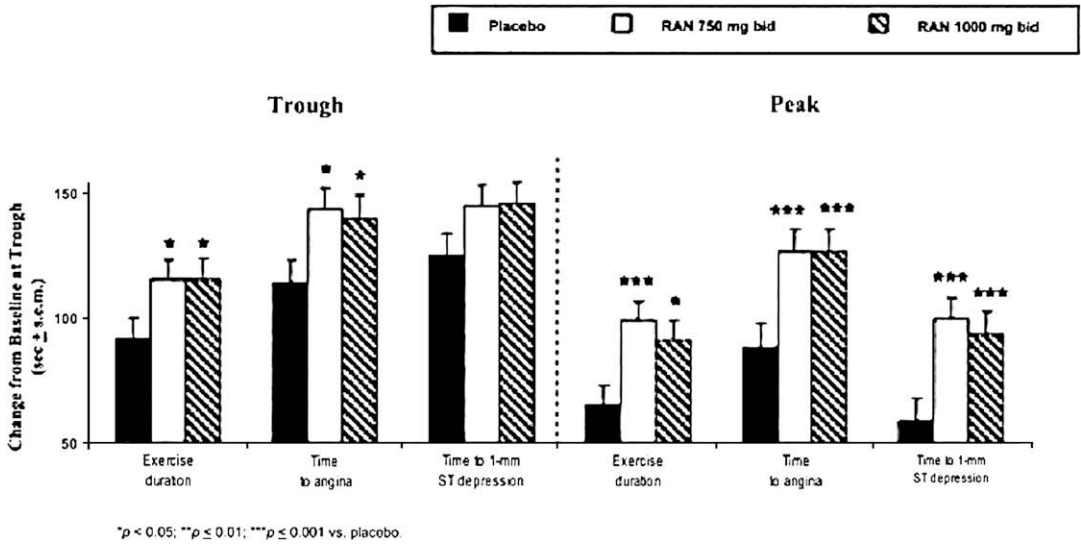


Fig. 7. Effect of ranolazine 1000 mg twice a day on exercise treadmill performance when combined with atenolol 50 mg every day, diltiazem 120 mg every day, or amlodipine 5 mg every day. (From Chaitman BR, Pepine CJ, Parker JO, et al. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. *Data from JAMA* 2004;291:312.)

in reduction in angina, nitroglycerin consumption, and Seattle Angina Questionnaire (Fig. 8).¹⁴ These results suggest that those patients who have the most frequent angina may have the most sustained left ventricular dysfunction from their repetitive bouts of ischemia, and that these patients are the ones most likely to experience a substantial benefit from ranolazine’s effects on ischemia-associated left ventricular dysfunction.

Unstable Angina/Non–ST Segment Elevation Myocardial Infarction

The recent MERLIN TIMI-36 trial addressed the value of an intravenous infusion of ranolazine, followed by oral ranolazine, in patients who had a non–ST segment elevation acute coronary syndrome (ACS).¹⁵ A total of 6560 patients who had either unstable angina or NSTEMI were enrolled within 48 hours of ischemic symptoms and were

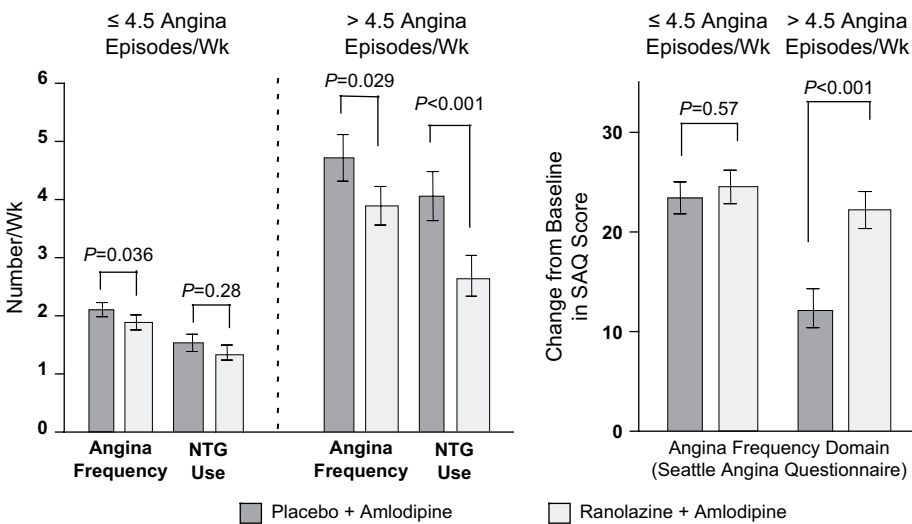


Fig. 8. Effect of ranolazine 1000 mg twice a day in patients who have refractory angina despite maximum amlodipine therapy: the ERICA trial. (From Stone PH, Gratsiansky NA, Blokhin A, et al. Antianginal efficacy of ranolazine when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine in Chronic Angina) trial. *J Am Coll Cardiol* 2006;48:572; with permission.)

treated with ranolazine (initiated intravenously and followed by oral ranolazine extended release 1000 mg twice a day) or matching placebo. They were followed up for a median of 348 days. The primary efficacy endpoint was a composite of cardiovascular death, myocardial infarction (MI), or recurrent ischemia and occurred in 21.8% of the ranolazine-treated patients and 23.5% of the placebo-treated patients (hazard ratio [HR] 0.92, 95% CI 0.83–1.02, $P = .11$) (Fig. 9A). Although there was no difference in the occurrence of the primary composite endpoint between the two treatment groups, or in two of the individual components of the primary composite endpoint (cardiovascular death or MI), there was a significant difference in the endpoint of recurrent ischemia (13.9% in the ranolazine-treated patients versus 16.1% in the placebo-treated group; HR 0.87, 95% CI 0.76–0.99, $P = .03$) (see Fig. 9B and Fig. 10). A trend toward an early reduction in recurrent ischemic complications with ranolazine was evident with respect to the 30-day endpoint of cardiovascular death, MI, severe recurrent ischemia, or positive Holter for ischemia ($P = .055$). An effect of long-term treatment with ranolazine on angina was evident with respect to several prespecified exploratory endpoints: reduction in worsening angina by at least one Canadian Cardiovascular Society class requiring intensification of medical therapy, less frequent escalation in antianginal medication, and improvement in anginal frequency using the Seattle Angina Questionnaire. There was no significant heterogeneity of the effect of ranolazine on the primary endpoint across the major subgroups examined.

Ranolazine also had a significant effect of preventing ventricular and atrial arrhythmias in these high-risk patients who had a non-ST elevation ACS,¹⁶ as discussed later.

In a substudy analysis stratifying patients on the basis of brain natriuretic peptide (BNP) measurements obtained at the time of randomization,

those patients who had an elevated BNP greater than 80 pg/mL, likely reflecting diastolic stiffness resulting from more severe or more prolonged ischemia, experienced a significantly higher incidence of cardiovascular death, MI, or recurrent ischemia compared with patients who had ACS with a BNP value less than 80 pg/mL ($P < .001$).¹⁷ Furthermore, ranolazine was associated with a significant reduction in the composite primary endpoint of cardiovascular death, MI, or recurrent ischemia in those high-risk patients who had an elevated BNP ($P = .009$), whereas there was no beneficial effect in low-risk patients who had a normal BNP value.¹⁷

The safety of ranolazine was confirmed in this large clinical trial. There was no difference in mortality between patients treated with ranolazine versus placebo, nor sudden death. The incidence of symptomatic documented arrhythmias throughout the duration of the study was also similar in the two treatment groups ($P = .84$). Discontinuation of treatment because of an adverse event occurred in 28% in the ranolazine group to 22% in the placebo group ($P < .001$). Discontinuation because of an adverse event was reported significantly more frequently among patients receiving ranolazine compared with patients receiving placebo (8.8% versus 4.7%, $P < .001$). The most frequent adverse events, occurring in more than 4% of patients, were dizziness (13% versus 7%), nausea (9% versus 6%), and constipation (9% versus 3%). Syncope occurred in 3.3% of the patients receiving ranolazine and 2.3% of the patients receiving placebo ($P = .01$). Most of these were believed to be vasovagal syncope. Only two cases of torsades de pointes were noted in the study, one in each treatment group.

Electrophysiologic Effects of Ranolazine and Efficacy as an Antiarrhythmic Agent

Ranolazine exerts several effects on cardiac ion currents at concentrations within the therapeutic

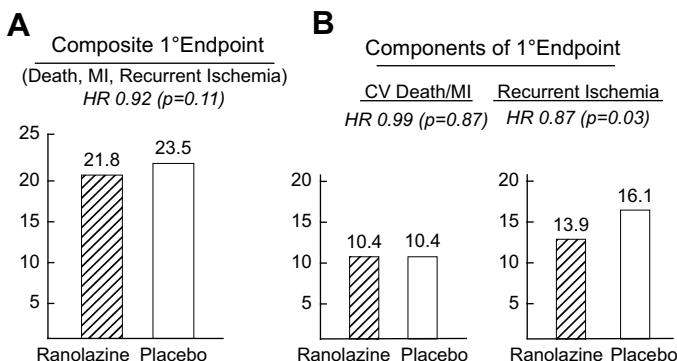


Fig. 9. Effect of ranolazine in patients who have a non-ST elevation ACS: the MERLIN trial. (From Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, et al. Effects of ranolazine on recurrent cardiovascular events in patients with non-ST elevation ACS: the MERLIN-TIMI 36 randomized trial. *Data from JAMA* 2007;297:1779.)

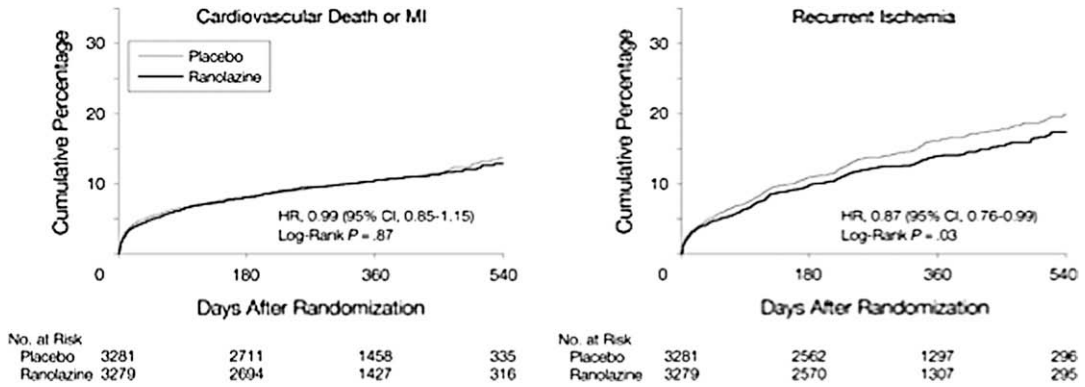


Fig. 10. Kaplan-Meier estimated rates of cardiovascular death or MI and recurrent ischemia. (From Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, et al. Effects of ranolazine on recurrent cardiovascular events in patients with non-ST elevation ACS: the MERLIN-TIMI 36 randomized trial. *JAMA* 2007;297:17780; with permission.)

range of 2 to 6 $\mu\text{mol/L}$, which include inhibition of I_{K_r} , late I_{Na} , and late $I_{Ca,L}$ (Fig. 11).⁶ Although inhibition of I_{K_r} by ranolazine prolongs the action potential duration, inhibition of the late I_{Na} and the late I_{Ca} shorten the action potential duration such that the net effect on the action potential duration, or QTc, is usually modest (ie, in the range of 5–10 milliseconds). In experimental animals and tissue preparations ranolazine actually shortens or normalizes the action potential duration that is prolonged from ischemia or exposure to arrhythmogenic compounds, such as d-sotalol (Fig. 12A, B).⁶

It is now well appreciated that development of drug-induced torsades de pointes requires not only prolongation of the action potential and the QTc interval, but also the presence of early afterdepolarizations and increased dispersion of repolarization across the myocardium. Although ranolazine exerts a minimal effect of prolonging

the QT interval, it exerts several other protective effects: (i) ranolazine reduces the incidence of early afterdepolarizations (see Fig. 12A), and (ii) ranolazine does not exacerbate the transmural dispersion of repolarization, which is associated with ischemia and exposure to arrhythmogenic drugs.⁶ In the experimental animal ranolazine does not cause torsades de pointes,⁶ and, as noted earlier in the experience in the MERLIN trial, there was only one case of torsades in the patients who had a non-ST elevation ACS, and this was the same incidence as in the placebo group.¹⁶

Although ranolazine has not been studied as a primary antiarrhythmic agent, it has been efficacious as an antiarrhythmic agent in the large-scale studies that have included continuous ECG monitoring.¹⁶ In the MERLIN trial 97% of the 6560 patients who had ACS had a continuous ECG that was interpretable for analysis. Treatment with ranolazine was associated with a significant reduction in ventricular arrhythmias, including ventricular tachycardia greater than or equal to 3, 4, or 8 beats at a rate of 100 beats per minute (bpm) or greater ($P < .001$), but had no effect on sustained ventricular tachycardia greater than 30 seconds (Table 2 and Fig. 13). Ranolazine also reduced the incidence of supraventricular arrhythmias 120 bpm or greater lasting 4 beats or more ($P < .001$), and was associated with a trend toward reducing the incidence of new-onset atrial fibrillation ($P = .08$) (see Table 2). Among several high-risk subgroups, including patients who had prior heart failure, reduced left ventricular function, prolonged QTc interval at baseline, and high TIMI Risk Score (5–7), ranolazine consistently reduced the incidence of ventricular tachycardias lasting 8 beats or more, although there was no difference in sudden cardiac death.¹⁶ Ranolazine also reduced the incidence of bradycardia less than

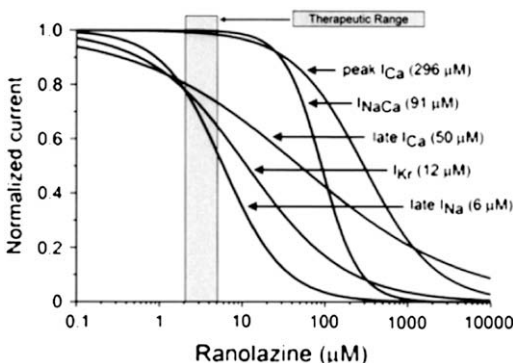


Fig. 11. Effect of ranolazine on electrophysiologic ion currents across the myocyte cell membrane. (From Antzelevitch C, Belardinelli L, Zygmunt AC, et al. Electrophysiological effects of ranolazine, a novel antianginal agent with antiarrhythmic properties. *Circulation* 2004;110:906; with permission.)

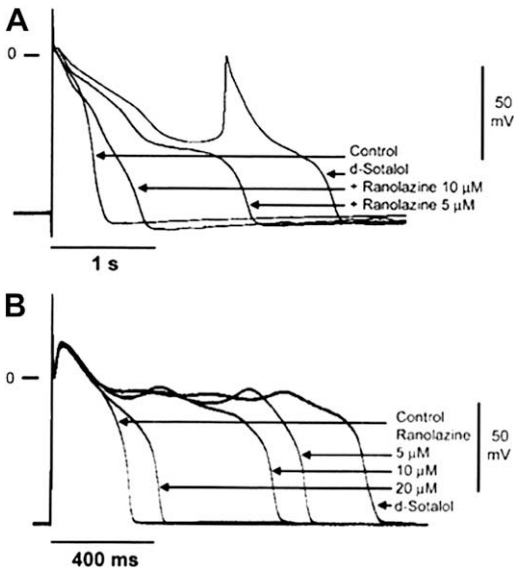


Fig. 12. Effect of ranolazine to normalize the action potential duration and suppress early afterdepolarizations in M cells (A) and Purkinje fiber preparations (B). (From Antzelevitch C, Belardinelli L, Zygmunt AC, et al. Electrophysiological effects of ranolazine, a novel antianginal agent with antiarrhythmic properties. *Circulation* 2004;110:909; with permission.)

45 bpm for at least 4 beats. It is not clear whether the antiarrhythmic effects observed with ranolazine were attributable to prevention of ischemia-associated arrhythmias by preventing the ischemia itself, or from a more primary antiarrhythmic effect related to its effect on membrane ion channels.

New studies are being considered to investigate the more primary use of ranolazine as an antiarrhythmic agent for atrial or ventricular arrhythmias.

Future Applications

Diastolic heart failure

Evidence in experimental animals suggests that ranolazine may provide a unique role in the management of patients who have heart failure, particularly diastolic heart failure associated with ischemic cardiomyopathy and left ventricular hypertrophy. Abnormal late I_{Na} , and subsequent sodium ion and calcium ion overload, is a common characteristic of myocardial dysfunction associated with myocardial ischemia, left ventricular hypertrophy, and various conditions associated with oxidative stress.⁴ Ranolazine is uniquely able to treat the abnormal late I_{Na} , and it can thereby prevent the sodium overload and the consequent calcium overload and the abnormal left ventricular diastolic function that ensues. For example, in isometrically contracting ventricular muscle strips from end-stage failing human hearts, ranolazine (10 μmol/L) significantly reduced the frequency-dependent increase in diastolic dysfunction by approximately 30% without significantly affecting sarcoplasmic reticulum Ca^{++} loading.¹⁸ To investigate the mechanism of this observed amelioration of diastolic dysfunction in the human heart, isolated ventricular rabbit myocytes were exposed to ATX-II, a toxin that mimics the effects of abnormal opening of the late I_{Na} , and ranolazine prevented the increases in late I_{Na} and intracellular sodium and diastolic calcium ions caused by ATX-II.¹⁸ In isolated ejecting/working

Table 2
Effect of ranolazine on tachyarrhythmias detected after non-ST segment elevation myocardial infarction

	Ranolazine n (%)	Placebo n (%)	RR (95% CI)	P value
Ventricular arrhythmias				
VT ≥ 3 beats ≥ 100 bpm	1646 (52.1)	1933 (60.6)	0.86 (0.82–0.90)	<0.001
VT ≥ 4 beats ≥ 100 bpm	662 (20.9)	941 (29.5)	0.71 (0.6–0.78)	<0.001
VT ≥ 8 beats (lasting <30 s)	166 (5.3)	265 (8.3)	0.63 (0.52–0.76)	<0.001
Polymorphic VT ≥ 8 beats	38 (1.2)	46 (1.4)	0.83 (0.54–1.28)	0.40
Sustained VT (≥ 30 s)	14 (0.44)	14 (0.44)	1.01 (0.48–2.13)	0.98
Monomorphic	4 (0.13)	7 (0.22)	0.59 (0.17–2.06)	0.37
Polymorphic	10 (0.32)	7 (0.22)	1.41 (0.52–3.78)	0.46
Supraventricular arrhythmias				
New-onset atrial fibrillation	55 (1.7)	75 (2.4)	0.74 (0.52–1.05)	0.08
Other SVT ≥ 120 bpm lasting at least 4 beats	1413 (44.7)	1752 (55.0)	0.81 (0.77–0.85)	<0.001

Abbreviations: bpm, beats per minute; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

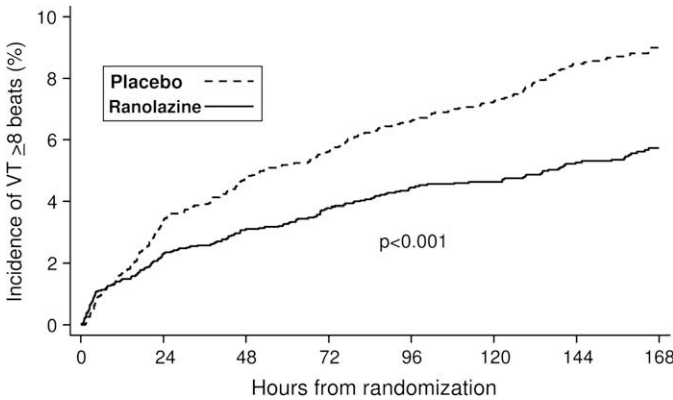


Fig. 13. Kaplan-Meier estimated rates of the first occurrence of an episode of ventricular tachycardia lasting at least 8 beats. The incidence of ventricular tachycardia was significantly lower in patients treated with ranolazine versus placebo at 24 hours after randomization (2.3% versus 3.4%; relative risk [RR], 0.67; 95% CI, 0.50–0.90; $P = .008$) and 48 hours (3.1% versus 4.7%; RR, 0.65; 95% CI, 0.51–0.84; $P < .001$). (From 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 ACS: 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* 2007;116:1650; with permission.)

rat hearts ranolazine prevents the left ventricular systolic and diastolic dysfunction associated with exposure to ischemia (Fig. 14).⁴ Similarly, isolated rat hearts exposed to hydrogen peroxide, the primary reactive oxygen species associated with detrimental oxidative stress, develop immediate diastolic dysfunction, which can be ameliorated by treatment with ranolazine.¹⁹

In intact animal models of heart failure ranolazine improves myocardial function. Sabbah and colleagues created chronic heart failure in dogs by intracoronary microembolizations (mean left ventricular ejection fraction 27%) and then administered ranolazine intravenously with a bolus and infusion (1.0 mg/kg/h).²⁰ Ranolazine significantly increased the ejection fraction (27% to 36%,

$P = .0001$), the peak left ventricle $+dP/dt$ (1712 to 1900 mm Hg/s, $P = .001$), and stroke volume (20 to 26 mL, $P = .0001$) without affecting heart rate or systemic pressure. Using this same model, these investigators subsequently demonstrated that both ranolazine and dobutamine infusions increased left ventricular ejection fraction, stroke volume, cardiac output, and peak $+dP/dt$, without affecting heart rate or systolic pressure, but that the improvement from ranolazine, in comparison to dobutamine, was related to an increase in left ventricular mechanical efficiency and not to an increase in coronary blood flow or myocardial O_2 consumption.²¹ Indices of diastolic dysfunction were not assessed in these studies. In contrast to these studies, Aaker and colleagues created

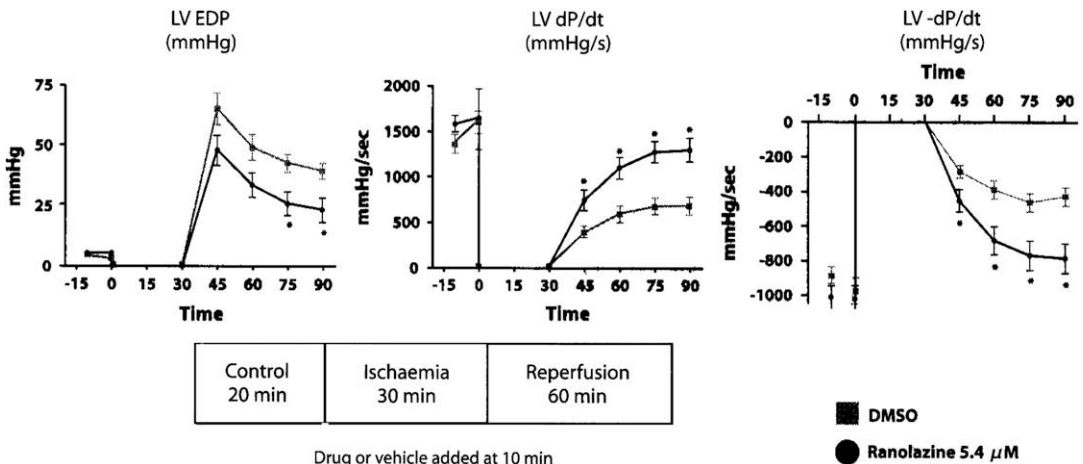


Fig. 14. Ranolazine prevents left ventricular systolic and diastolic dysfunction caused by ischemia in rabbit isolated Langendorff perfused hearts. (From Belardinelli L, Antzelevitch C, Fraser H. Inhibition of late (sustained/persistent) sodium current: a potential drug target to reduce intracellular sodium-dependent calcium overload and its detrimental effects on cardiomyocyte function. *European Heart Journal* 2004;6:16; with permission.)

chronic heart failure in rats by surgically inducing an MI, and then administered ranolazine 50 mg/kg twice a day.²² They observed that ranolazine did not increase the endurance capacity in these animals, but the doses used in this study were almost 10 times the usual dose in humans.

Preliminary studies in humans suggest that ranolazine may be of clinical usefulness in the management of patients who have diastolic dysfunction associated with ischemic cardiomyopathy. Hayashida and colleagues²³ administered intravenous ranolazine 200 or 500 μ g/kg to 15 patients who had previous transmural MI in whom regional left ventricular segments were classified as either normal, ischemia, or infarcted. Administration of ranolazine significantly increased the regional peak filling rate and the regional wall lengthening during the isovolumic relaxation period in the ischemic segments ($P < .05$), indicating an improvement of regional diastolic function, without significant effect on the infarcted segments. Early preliminary experience suggested that ranolazine immediate-release formulation improved the peak filling rate as assessed by echo Doppler analysis of the left ventricular filling dynamics.²⁴ Similarly, intravenous administration of ranolazine to 15 patients who had ischemic cardiomyopathy led to a significant downward shift of the pressure–volume relationship during diastole accompanied by a reduction in mean diastolic wall stress and increase in end-diastolic volume.²⁵ A recent preliminary study investigating the proof-of-concept of the effects of ranolazine in patients who had a documented genetic defect in the late sodium channel, the hereditary long QT syndrome LQT3-deltaKPKQ, found that intravenous ranolazine shortened the prolonged QTc and significantly improved the associated diastolic dysfunction, as assessed by the left ventricular isovolumic relaxation time and the mitral E-wave velocity.²⁶

Further studies in humans investigating the role of ranolazine in treating diastolic dysfunction are ongoing and the results are awaited with great interest.

SUMMARY

Ranolazine is a new compound that has been approved by the FDA for use in patients who have chronic stable angina refractory to conventional antianginal medications. Its mechanism of action does not depend on lowering determinants of myocardial O₂ demand, which is the mechanism used by conventional anti-ischemic medications, but instead it prevents the pathologic persistent opening of the late I_{Na} current, which occurs

when the myocardium is exposed to ischemia, heart failure, and oxidative stress. Ranolazine thereby prevents the intracellular sodium and subsequent calcium overload that occurs in these disorders, and the associated myocardial metabolic, electrophysiologic, and mechanical dysfunction. Ranolazine consequently improves diastolic and systolic left ventricular function and preserves myocardial perfusion.

Ranolazine is effective as monotherapy for patients who have stable angina and also effective as part of a combination regimen. In non-ST elevation ACS it reduces recurrent ischemia and ventricular and atrial arrhythmias, but has no effect on mortality or development of MI.

In animal models of heart failure and in preliminary studies in humans, ranolazine improves diastolic and systolic dysfunction.

More studies are needed to evaluate the role of ranolazine as primary therapy for myocardial diastolic and systolic dysfunction and ventricular and atrial arrhythmias.

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