Chronic Angina: New Medical Options for Treatment

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As the US population ages, the pool of patients with coronary artery disease and stable angina is projected to grow. Conventional approaches with mechanical and pharmacological therapies have made inroads toward curbing this trend, reducing the risk of future myocardial infarction and cardiac death. However, the potential benefits of currently available antianginal medications are limited by reduced work capacity, orthostasis, and important drug-drug interactions. A new approach is represented by the piperazine derivatives trimetazidine (TMZ) and ranolazine (RNZ). TMZ acts to partially inhibit fatty acid oxidation, thus shifting myocardial energy metabolism to a lower oxygen-consuming state. A total of 16 randomized trials have been completed with TMZ. In the US market, 6 trials have been completed with RNZ. RNZ has been separately classified as a late sodium channel inhibitor, which reverses action potential prolongation, suppresses early after-depolarizations, and terminates resultant ventricular tachycardia. Though it has some of the same fatty acid oxidation properties as TMZ, this is not considered its primary mechanism of action. This paper reviews medical approaches to chronic stable angina and highlights RNZ as an important advance for patients and clinicians in the US market.

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Chronic stable angina pectoris can manifest as predictable and reproducible chest-discomfort symptoms related to exercise, physical exertion during activities of daily living, sexual activity, and emotional stress. Symptoms are often exacerbated by cold weather or heavy meals. Symptoms improve with rest or with sublingual nitroglycerin therapy. However, it is known that coronary insufficiency can have a wide array of stable symptoms including atypical chest discomfort; epigastric, neck, arm, or back pain;

diaphoresis; shortness of breath; and nausea. Women, the elderly, and the ever-increasing pool of patients with diabetes are more likely to have these atypical manifestations of chronic stable angina. Angina occurs in the event of regional myocardial ischemia caused by mismatch between myocardial oxygen delivery and the metabolic demand for oxygen. There is no correlation between the severity of angina and the severity of coronary disease.[1]

As coronary atherosclerosis progresses, there is deposition of plaque external to the lumen of the artery; the plaque may extend eccentrically and outward without compromising the lumen. The best understood anatomic mechanism for angina is epicardial coronary vessel luminal narrowing, usually greater than 70%, resulting in reductions of flow and an inability to expand the coronary reserve in response to increased oxygen demand. However, it is now understood that there can be many combinations of epicardial disease involving more than one vessel, small vessels, microvascular abnormalities including regional vasoconstriction, and heightened states of cardiac awareness, all of which can complicate and confound diagnosis.[2] Vulnerable plaque within the vessel wall may not be obstructive and may remain clinically silent until rupturing and the associated consequences occur. The process of asymptomatic plaque rupture, repair, and arterial remodeling is thought to occur in patients who are asymptomatic and in those with chronic stable angina. Only when there is significant or complete occlusion of the vessel or downstream embolization of thrombotic material does an acute coronary syndrome develop. In the United States, most patients with chronic stable angina have had prior revascularization, and many have had maximal revascularization efforts. Among a pool of millions with coronary disease, it is estimated that 6 to 7 million US patients have angina. Approximately 300,000 to 900,000 have refractory anginal symptoms, and the pool of patients expands by 25,000 to 75,000 new cases each year.[3] Hence, the role of pharmacotherapy in managing symptoms and improving functional capacity is of paramount concern.

Improving the Natural History of Coronary Disease

There is considerable evidence that lifestyle changes and pharmacologic therapy may reduce the progression of atherosclerosis, stabilize plaque, or both, in patients with chronic stable angina.[4] The vast majority of patients with coronary heart disease have at least one modifiable cardiac risk factor.[5] Obesity and sedentary lifestyle are both recognized as common, major cardiac risk factors. Excess adiposity is increasingly recognized as a pro-inflammatory and directly atherogenic state.[6] For the majority of patients with coronary disease, excess adiposity is directly causative or heavily contributory to their disease. A recent report indicated that among patients with severe, refractory stable angina symptoms, obesity (body mass index [BMI] > 30 kg/m^2) was common (40.6%). In addition, 4.5% of these patients were morbidly obese (BMI > 40 kg/m^2).[7] Excess adiposity is unique in that it is the only central, modifiable factor in the natural history of atherosclerosis. In other words, as the level of adiposity is lessened, virtually all other cardiac risk factors improve, including blood pressure and lipid levels, diabetic control, physical activity levels, and measures of systemic inflammation. Hence, reduction in adiposity should be a primary strategy for reducing coronary risk factors and a base upon which mechanical and pharmacologic strategies are added.

Both percutaneous coronary intervention and coronary artery bypass surgery offer patients the opportunity to reduce angina severity, improve functional capacity, and reduce mortality in certain subsets. In the setting of multivessel disease, clinical trials suggest that there is a tradeoff between multivessel PCI requiring more procedures over time versus bypass surgery, which is more invasive but offers a greater post-procedure period free from additional surgeries.[2] Enhanced external counterpulsation (EECP) is also a proven mechanical treatment for chronic stable angina and appears to improve anginal symptoms after 7 weeks of treatment, irrespective of the background medical therapy used.[8] This paper will not deal with revascularization or EECP further. However, it is recognized that medical strategies are complementary and often utilized in addition to these approaches.

Vasculoprotective Pharmacologic Therapy

Oral agents that have been shown to reduce rates of myocardial infarction, cardiac death, and potentially provide "vascular" protection are shown in Table 1. The use of aspirin at a dose of 81 to 150 mg per day reduces cardiovascular morbidity and mortality by 20% to 25% among patients with coronary artery disease.[4] The results of several large, randomized trials indicate that the use of statins reduces the rate of coronary events and mortality in patients with established coronary artery disease and hyperlipidemia by 25% to 35%.[4] Furthermore, a 25% to 30% reduction in revascularization rates in the large statin trials suggests that statin therapy lessens the severity of angina,

Table 1
Vasculoprotective Agents for Patients with Chronic Stable Angina

Agent	Indications	Comment
Aspirin	All patients, except those with aspirin allergy or resistance	Dosage, 81-150 mg daily or 325 mg every other day
Statin	All patients, to achieve target LDL cholesterol level ≤100 mg/dl; goal of 70 mg/dl in very high-risk patients (those with diabetes, multivessel disease, or multiple risk factors for coronary artery disease)	May use C-reactive protein level to guide dosage, with target <2 mg/liter, although this strategy has not been tested
β-blocker	All patients with exertion-related or emotion-related chest pain, previous MI, hypertension, depressed left ventricular function (in absence of contraindication)	
Clopidogrel	All patients after PCI or those with aspirin intolerance or resistance	Duration of therapy, 1 year after PCI, indefinitely if aspirin cannot be used
ACE inhibitor	High-risk patients: those with diabetes, chronic kidney disease, hypertension, previous MI, left ventricular systolic dysfunction, or age ≥55 yr	Uncertain utility in low-risk patients

LDL, low-density lipoprotein; MI, myocardial infarction; PCI, percutaneous coronary intervention; ACE, angiotensin-converting enzyme. Reproduced with permission from Abrams.[2]

and hence there is less ischemia-driven revascularization.[2] Fixed, high-dose statins have been shown to further reduce the rates of cardiovascular events in patients with coronary disease, irrespective of baseline low-density lipoprotein cholesterol (LDL-C) levels.[2] The Adult Treatment Panel III of the National Cholesterol Education Program recently recommended target LDL-C levels of 60 mg/dL to 70 mg/dL in high-risk patients with coronary artery disease.[9] Angiotensin-converting enzyme (ACE) inhibitors have been reported to reduce morbidity and mortality among patients with coronary disease when the annual event rate (nonfatal MI or cardiovascular death) exceeds 1%.[10-11] Patients are particularly likely to benefit from ACE inhibitor therapy if there is a history of MI, hypertension, left ventricular systolic dysfunction, diabetes, or chronic kidney disease.

Improving Anginal Symptoms and Functional Capacity

Conventional Antianginal (Anti-Ischemic) Agents

All conventional antianginal drugs including nitrates, β-adrenergic blockers, and calcium-channel blockers have been shown to decrease anginal frequency and prolong the duration of exercise before electrocardiographic evidence of ischemia is detected.[2] Conventional oral antianginal agents are shown in Table 2. Treadmill performance typically increases by 30 to 60 seconds in patients treated with antianginal drugs (as monotherapy) when compared to performance with placebo. Head-to-head comparative trials have not demonstrated the superiority of any single class of agents.[2] β-Blockers work primarily by decreasing myocardial oxygen consumption through reductions in heart rate, blood pressure, and myocardial contractility. β-Blockers are considered class I drugs, according to the 2002 American College of Cardiology/American Heart Association Guideline Update for the Management of Patients With Chronic Stable Angina.[4] This classification is based on older trials showing that these agents prolong survival after myocardial infarction and on recent data showing that they have a similar benefit after primary angioplasty for acute non–ST-elevation myocardial infarction.[4] There have been no large trials assessing the effects of β-blockers on survival or on rates of coronary events in patients with chronic stable angina. Fatigue, depression, sexual dysfunction, and glucose intolerance are all common side effects of β-blockers.

Calcium antagonists dilate coronary and systemic arteries, increase coronary blood flow, and decrease myocardial oxygen consumption. Fatigue, constipation, and lower extremity edema are common side effects with calcium antagonists.[2] Nitrates dilate systemic and coronary arteries and systemic veins. Sublingual or oral spray nitroglycerin relieves acute episodes of angina within 5 to 10 minutes; prophylactic use before activity can be helpful in persons with frequent angina.[2] Although long-acting nitrates decrease angina and prolong exercise performance, significant tolerance can develop. Acute orthostasis at the time of use and headaches are the most common

Table 2
Conventional Antianginal Agents

Drug Class and Drug	Dosage Range	Adverse Effects	Cautions
Nitrates[†]			
Isosorbide dinitrate, short-acting formulations	20-60 mg twice daily	Headaches, dizziness, nausea, palpitations	Contraindicated with medications for erectile dysfunction
Isosorbide dinitrate, sustained-release formulations	60-120 mg once daily	Tolerance is a major limiting factor	
Isosorbide mononitrate, short-acting formulations	20 mg twice daily, 7 hr apart		
Isosorbide mononitrate, sustained-release formulations	60-120 mg once daily		
Nitroglycerin, patch	0.4-0.6 mg, taken for no more than 12-14 hr		
Beta-adrenergic blockers			
Propranolol, long-acting formulations	80-240 mg once daily	Fatigue, shortness of breath, wheezing, weakness, dizziness	Should be used with caution in patients with chronic obstructive pulmonary disease, diabetes, depression, severe peripheral vascular disease, coronary vasospasm, sinus or atrioventricular nodal dysfunction, or erectile dysfunction
Metoprolol, short-acting formulations	50-150 mg twice daily		
Metoprolol, sustained-release formulations	100-300 mg once daily		
Atenolol	25-100 mg once daily		
Calcium-channel blockers			
Nifedipine, sustained release formulations	30-90 mg once daily	Headache, dizziness, edema	Verapamil and diltiazem should be used with caution in patients with low ejection fraction (<30%) or with sinus or atrioventricular nodal dysfunction
Amlodipine	2.5-10 mg once daily		
Verapamil, short-acting formulations	40-120 mg 2-3 times daily	Constipation (with verapamil)	
Verapamil, sustained-release formulations	180-240 mg once or twice daily		
Diltiazem, sustained-release formulations	120-480 mg once daily		

Recommended combination therapies include a nitrate with a beta-blocker and a dihydropyridine calcium-channel blocker with a beta-blocker. The combination of a dihydropyridine calcium-channel blocker with a nitrate or the combination of a rate-slowing calcium-channel blocker with a beta-blocker is not recommended. [†]A nitrate-free interval of 12 to 14 hours daily is necessary. Reproduced with permission from Abrams.[2]

side effects with nitrate therapy. In addition, phosphodiesterase type 5 inhibitors (eg, sildenafil, vardenafil, and tadalafil) should not be used within 24 hours of nitrate administration because of the potential for serious hypotension. Even after maximum mechanical/surgical revascularization, many patients require multiple antianginal agents but hypotension, bradycardia, and reduced exercise work capacity limit the use of these combinations.

Unconventional Agents

Other pharmacological agents that have been used to control chronic angina include ivabradine, nicorandil, L-arginine, testosterone, and estrogen.[3] These approaches have not gained popularity in the United States, due to either excess side effects or lack of large prospective randomized trials demonstrating efficacy.

Cellular Metabolic Agents

As discussed above, the conventional antianginal agents work to reduce myocardial oxygen demands or improve oxygen supply through improved perfusion. A new approach focuses on the energy metabolism of the cardiomyocyte itself by reducing

the oxygen cost of adenosine triphosphate production.[12] This goal can be achieved by shifting energy production from fatty acid β-oxidation to glucose oxidation, thus increasing pyruvate oxidation and reducing anaerobic glycolysis. High fatty acid levels result in oxygen wasting and inhibit the oxidation of pyruvate in the mitochondria. In experimental models, the partial inhibition of myocardial fatty acid oxidation with agents such as oxfenicine, ranolazine (RNZ), and trimetazidine (TMZ) stimulates glucose oxidation and reduces lactate production during ischemia.[12,13] The differing chemical structures of TMZ and RNZ, which are both piperazine derivatives, are given in Figure 1.

Trimetazidine

TMZ (1-[2,3,4-trimethoxibenzyl]-piperazine) is the first and only registered drug in this class, and is available in over 90 countries worldwide (Figure 1). Trimetazidine selectively inhibits the fatty acid β-oxidation enzyme 3-keto-acyl-CoA dehydrogenase (3-KAT).[14] Table 3 summarizes 12 trials of TMZ in a meta-analysis spanning from 1985 to 2001 and 4 trials from 2002 to 2005, all in patients with chronic stable angina.[15-19] These trials were double-blind, randomized, placebo or usual-care controlled, with TMZ used as mono- or add-on therapy. TMZ significantly improved symptom-limited exercise performance in stable angina patients when used either as monotherapy or in combination with β-blockers or calcium channel blockers. TMZ has no effect on the corrected QT interval.[14] Trimetazidine does not suppress

Table 3
Randomized, Controlled Trials of Oral Trimetazidine (TMZ)

Study	N	Comparison	Duration	Results
Chazov et al.[15]	177 stable angina patients 52% of patients received long-acting nitrates, and 48% were treated with a β-blocker as monotherapy (6-centers in Russia)	TMZ 20 mg tid (n = 90) vs placebo (n = 87)	12 weeks	TMZ ↑ exercise duration by 90 sec vs 24 sec ↑ time to ST depression 91 sec vs 17 sec ↓ anginal frequency All $P < 0.05$
Koylan et al.[16]	116 male patients with documented coronary artery disease at 11 centers	TMZ 20 mg tid vs Diltiazem	4 weeks	Both ↓ anginal frequency ↓ nitrate consumption ↑ recovery of anginal pain ↓ maximal ST-segment depression All $P < 0.05$ ↔ ST-segment depression ↔ ST recovery time on exercise test.
Sellier et al.[17]	167/223 evaluable patients class II-III angina, all on atenolol 50 mg qd (multicenter, multinational)	TMZ Modified Release (MR) 35 mg bid vs placebo	8 weeks	TMZ ↑ time to ST segment depression 44 sec ↑ time to angina All $P < 0.05$
Manchanda et al.[18]	N = 50, stable angina, all on diltiazem 90 mg qd (single center in India)	TMZ 20 tid (n = 25) vs placebo (n = 25)	4 weeks	TMZ ↑ time to 1-mm ST depression by 128 sec ↓ Duke treadmill score of 57.4% ↓ Anginal frequency All $P < 0.05$
Marzilli and Klein[19]	1985-2003 meta-analysis of 12 trials	TMZ vs placebo/ comparators	≥2 weeks	TMZ ↓ Anginal frequency ↑ Time to ST-depression All pooled $P < 0.05$

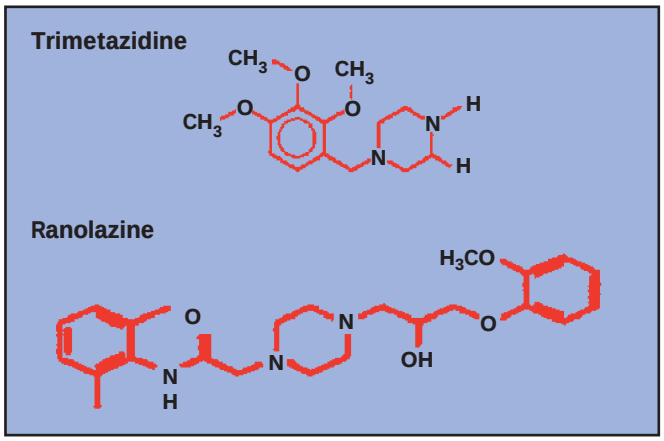

Figure 1. *Differing chemical structures of the piperazine derivatives, trimetazidine and ranolazine.*

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heart rate, blood pressure, or contractility; hence it is used frequently outside the United States in combination with conventional antianginal agents. In the United States, RNZ is furthest along in clinical development and will be the focus of the remainder of this review.

Ranolazine

Ranolazine (Ranexa™; CV Therapeutics, Inc., Palo Alto, CA) is a piperazine derivative with anti-ischemic properties attributed to the selective inhibition of late sodium current in ventricular myocytes. However, the mechanism of action of this agent is not yet fully understood. RNZ has also been shown to partially inhibit fatty acid oxidation, thereby increasing glucose oxidation and generating more ATP per molecule of oxygen consumed. However, this effect is now considered obtainable at relatively high does and thus marginal in terms of overall clinical mechanism.

Unlike TMZ, RNZ also has important electrophysiological effects on cardiomyocytes. It blocks to varying degrees the I(Kr), late I(Na), late I(Ca), peak I(Ca), I(Na-Ca) and I(Ks) channels, but causes little or no inhibition of I(to) or I(K1) channels. In left ventricular tissue preparations, RNZ produces a concentration-dependent prolongation of the action potential in epicardial cells, and shortens the action potential of mid-myocardial cells, leading to either no change or a reduction in transmural dispersion of repolarization.[20] The result is a minimal prolongation of the QT interval by 5-14 milliseconds (~1%-3%). QT prolongation with RNZ is rate-independent and is not associated with early after-depolarizations, triggered activity, or polymorphic ventricular tachycardia (torsade de pointes), unlike other drugs that block I(Kr), such as d-sotalol. In fact, RNZ promotes significant antiarrhythmic activity, which appears to counter the proarrhythmic effect of other QT-prolonging drugs. Ranolazine produces ion channel effects similar to those observed after chronic exposure to amiodarone (reduced late I[Na], I[Kr], I[Ks], and I[Ca]). The effect of RNZ, reducing the dispersion of repolarization and suppressing early after-depolarization, suggests that this agent may potentially reduce the arrhythmic potential of cardiac ischemia and possibly work to reduce the proarrhythmic effect of other agents.[20]

RNZ taken orally maintains a 30% to 55% bioavailability, and absorption is not affected by food. The half life of the immediate release form is 2 hours and it is metabolized by the cytochrome P-450 3A4 system.[13] The sustained release formulation is dosed every 12 hours. RNZ is capable of producing anti-ischemic effects at plasma concentrations of 2 to 6 µmol without a significant reduction of heart rate or blood pressure. There have been no observed spontaneous arrhythmias at concentrations up to 100 µmol. Drug levels have been increased 2- to 4-fold with concomitant diltiazem, inhibitors of the cytochrome P-450 3A4 system, and moderate hepatic and severe renal (estimated glomerular filtration rate < 30 mL/min) dysfunction. Ranolazine has not been associated with liver and renal toxicity. The most common side effects include gastrointestinal complaints, headache, dizziness, and fatigue.[13]

Table 4 summarizes the 6 prospective, randomized trials completed with RNZ.[21-26] Exercise stress tests were used to evaluate and all patients were required to have angina and reproducible stress tests demonstrating 1 mm ST-segment depression or greater, at peak stress. The stress tests were done at peak, trough, and in some cases at both times in the drug metabolism cycle. In general, tests done at RNZ peak have an approximately 7% increased time in exercise duration and time to ST-depression (most objective measures) compared to tests done at trough RNZ level.[22] At very low doses, there has been no effect on the duration of treadmill time or the time to ST-segment depression, suggesting a biological threshold response between dose, drug level achieved, and relief of angina.[22,25] Figure 2 demonstrates the relationships between RNZ dose, achieved plasma level, and improvement in exercise duration over placebo.[22] This agent appears to be the only anti-ischemic drug that can be assayed in blood and its levels predictably related to symptom response. In a head-to-head trial of RNZ (400 mg po, tid) versus atenolol

Table 4
Randomized, Controlled Trials of Oral Ranolazine (RNZ) in Chronic Stable Angina

Study	N	Comparison	Duration	Results
Rousseau et al.[21]	158 chronic stable angina taken off β blockers, 54% on CCB, 11% on nitrates	3-period, double-blind crossover study of immediate release (IR) RNZ 400 mg tid, atenolol (A) 100 mg qd or placebo (P), each administered for 1 week.	1 week	RNZ (at peak) ↑ exercise duration by 37 sec RNZ vs P by 16 sec A vs P ↑ time to ST-dep by 53 sec RNZ vs P by 51 sec A vs P all $P < 0.05$ RNZ ↔ HR, DP, SBP
Chaitman et al.[22]	191 chronic stable angina taken off baseline anti-anginal drugs	4-period, double-blind four-period crossover study of sustained-release RNZ 500, 1,000, or 1,500 mg, or placebo, each bid for one week	1 week	RNZ (at trough) ↑ exercise duration over placebo by 24 sec with 500 mg bid by 33 sec with 1,000 mg bid by 46 sec with 1,500 mg bid ↑ time to ST-dep all $P < 0.05$ ↔ HR, DP, SBP
Chaitman et al.[23]	823 chronic stable angina receiving standard doses of atenolol (43%), amlodipine (31%), or diltiazem (26%), multicenter, multi-national	A randomized, 3-group parallel, double-blind, sustained release RNZ 750 mg bid, RNZ 1000 mg bid, placebo	12 weeks	RNZ (at trough) ↑ exercise duration over P by 24 sec RNZ 750 bid by 24 sec RNZ 1000 bid ↑ time to ST-dep by 20 sec RNZ 750 bid by 21 sec RNZ 1000 bid ↓ Anginal attacks/wk 3.3 P 2.5 RNZ 750 bid 2.1 RNZ 1000 bid
Pepine and Wolff[24]	312 chronic stable angina, with at least one antianginal drug withdrawn, 34% on β-blocker 24% on CCB, none on NTG multicenter	Double-blind, randomized to RNZ-IR, 300 mg bid, 267 tid, 400 mg p.o. tid, or placebo (double-dummy latin square design)	1 week	RNZ (peak) ↑ exercise duration by 10 sec 300 bid by 12 sec 267 tid by 10 sec 400 tid ↑ time to ST-dep by 17 sec 300 bid by 25 sec 267 tid by 22 sec 400 tid all $P < 0.05$
Thadani et al.[25]	319 chronic stable angina, taken off all anti-anginals	Double-blind, randomized to RNZ-IR 30 mg tid (n = 81), RNZ-IR 60 mg tid (n = 81), RNZ-IR 120 mg tid (n = 78), and placebo tid (n = 79).	4 weeks	RNZ (at peak and trough) no differences versus placebo in total exercise time.
Cocco et al.[26]	104 stable angina pectoris	Double-blind, crossover, randomized study comparing placebo with a single dose of immediate release RNZ 10, 60, 120, and 240 mg	Single dose	RNZ at 240 mg dose only ↑ 13.1% in the combined group, two-tailed P = 0.002 ↑ time to ST-segment depression All $P < 0.05$

CCB, calcium channel blocker; SBP, systolic blood pressure; NTG, nitroglycerin; DP, diastolic pressure; HR, heart rate.

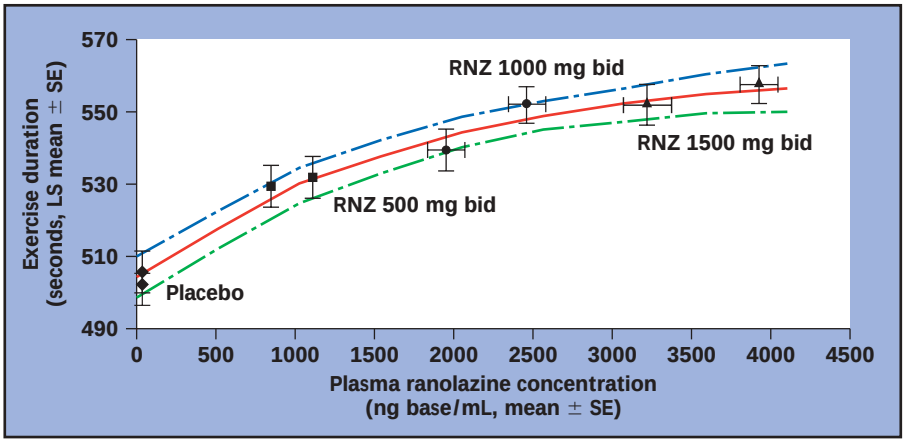


Figure 2. *Improvement in exercise duration according to achieved plasma concentration of ranolazine (RNZ) in the MARISA trial. LS, least squares; SE, standard error.* www.medreviews.com

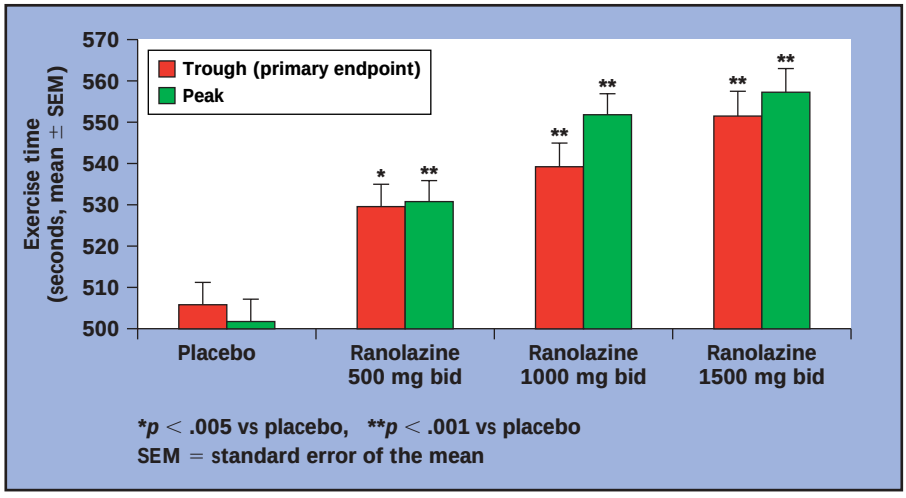
(100 mg po, qd), n = 158, RNZ improved exercise duration by 21.1 seconds ($P = 0.006$).[21] Importantly, the rate-pressure product was higher in the RNZ group compared to atenolol, suggesting RNZ facilitated a greater work capacity than that achieved with atenolol.

In the Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) trial, 191 patients with chronic stable angina were randomized to sustained release RNZ at 500 mg, 1000 mg, or 1500 mg, versus placebo, given twice daily for one week (4 period design).[22] Patients with chronic stable angina of at least 3-months duration were required to have exercise-induced angina and reproducible ST segment depression of 1 mm or greater on exercise treadmill testing, performed on 2 occasions. Exclusion criteria included a corrected QT interval greater than 500 msec. The primary endpoint was exercise stress test duration. The secondary endpoint was the time to 1 mm ST depression or greater. Measurements were made at both peak and trough level of the drug. There was a graded improvement in exercise duration related to the dose of RNZ as shown in Figure 3.[22] A subgroup with prior heart failure (HF) showed greater relative benefit with RNZ compared to placebo. In this trial, 143 patients were allowed to continue open-label RNZ for treatment of angina. The 1-year survival rate was 96.3% and there were no safety issues found during prolonged therapy. This survival rate is similar to that previously reported in patients with coronary artery disease and preserved left ventricular function.

The Combination Assessment of Ranolazine in Stable Angina (CARISA) trial randomized patients with chronic stable angina who remained on background anti-anginal therapy to placebo (n = 269), RNZ (750 mg, po, bid, n = 279) or RNZ (1000 mg, po, bid, n = 279) for 12 weeks.[23] Background therapy included atenolol in 43%, amlodipine in 86%, and diltiazem in 26%. Stress testing was done at peak and trough RNZ levels. There was a progressive improvement in exercise duration with both doses of RNZ at 2, 6, and 12 weeks. The frequency of anginal attacks and the use of short-acting nitroglycerin were also reduced with RNZ, when compared to the placebo group. Of note, at 1000 mg (po, bid) RNZ reduced systolic blood pressure by approximately 3 mm Hg. In patients with diabetes, RNZ was associated with a small (~0.5%) absolute

In the CARISA Trial, there was a progressive improvement in exercise duration with both doses of RNZ at 2, 6, and 12 weeks.

Figure 3. *Total exercise time according to dose of RNZ at peak and trough concentrations in the MARISA trial.*



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reduction in glycohemoglobin, suggesting the long-term use of this agent may have allowed for greater physical activity on a daily basis with improved systemic insulin sensitivity.

The short-term pivotal outcomes trial Evaluation of Ranolazine in Chronic Angina (ERICA) has completed randomizing approximately 500 patients with chronic stable angina to RNZ (1000 mg, po, bid) versus placebo for 6 weeks. This trial is measuring anginal frequency as the primary endpoint. The Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Segment Elevation Acute Coronary Syndromes (TIMI-36 MERLIN) is a large scale trial of RNZ versus placebo in approximately 5500 patients with acute coronary syndromes at approximately 600 sites. In this trial, intravenous RNZ will be used in the first up-to-96 hours and then patients will be converted to oral RNZ and followed over time. This trial will be an excellent opportunity to evaluate both the long-term anti-ischemic effects of RNZ and its potential to reduce arrhythmias in patients at risk.

In general, when RNZ is used as monotherapy, it increases total exercise duration and time to ischemic ST-depression to a similar degree as conventional antianginal medications. When used as an add-on therapy, it further increases exercise capacity and reduces the frequency of anginal episodes on a weekly basis. These data are encouraging for patients with chronic stable angina, as β-blockers, calcium channel blockers, and nitroglycerin combinations have escalating side effects and work to reduce exercise capacity. In addition, RNZ minimally increases the QT interval, but in doing so is not proarrhythmic and, in fact, may have desirable antiarrhythmic effects in a variety of clinical scenarios. Furthermore, reductions in angina have been linked to reduced hospitalizations and improved mortality over the long-term in patients with coronary disease.

Summary

Chronic stable angina is a common and difficult-to-manage problem when patients fail to respond to conventional therapy. The most promising agent in development for the US market is RNZ, a late sodium channel blocker, which also has unique and desirable electrophysiologic properties. This agent is likely to become

Main Points

- Among a pool of millions with coronary disease, it is estimated that 6 to 7 million US patients have angina, approximately 300,000 to 900,000 have refractory anginal symptoms, and the pool of patients expands by 25,000 to 75,000 new cases each year.
- Steps to reduce excess adiposity as well as procedures including percutaneous coronary intervention, coronary artery bypass graft, and enhanced external counterpulsation therapy are all coupled with medical therapy to reduce the severity of angina and improve the natural course of coronary disease.
- β-Blockers are considered class I drugs, according to the 2002 American College of Cardiology/American Heart Association Guideline Update for the Management of Patients With Chronic Stable Angina. However, there have been no large trials assessing the effects of β-blockers on survival or on rates of coronary events in patients with chronic stable angina and fatigue, depression, sexual dysfunction, and glucose intolerance are all common side effects of β-blockers.
- Calcium antagonists and nitrates are also considered useful anti-anginal agents but are often required in combination, even after maximal mechanical/surgical revascularization, a practice limited by side effects of hypotension, bradycardia, and reduced exercise work capacity.
- Cellular metabolic agents offer a new approach in anti-anginal therapy, focusing on the energy metabolism of the cardiomyocyte itself by reducing the oxygen cost of adenosine triphosphate production.
- Ranolazine is a piperazine derivative with anti-ischemic properties attributed to modulation of late sodium channel current and electrophysiologic response.
- Ranolazine therapy causes a minimal prolongation of the QT interval by 5-14 milliseconds (~1%-3%), which is rate-independent and is not associated with early after-depolarizations, triggered activity, or polymorphic ventricular tachycardia (torsade de pointes). In fact, RNZ promotes significant antiarrhythmic activity, which appears to counter the proarrhythmic effect of other QT-prolonging drugs.
- In general, when ranolazine is used as monotherapy, it increases total exercise duration and time to ischemic ST-depression to a similar degree as conventional antianginal medications. When used as an add-on therapy, it further increases exercise capacity and reduces the frequency of anginal episodes on a weekly basis.

standard therapy for chronic stable angina and may play a future role in the management of acute coronary syndromes. ■

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