Novel Therapeutic Approaches to Treating Chronic Angina in the Setting of Chronic Ischemic Heart Disease

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Summary

Pharmacologic therapy to alleviate symptoms in chronic angina has been enhanced by the recent approval of several novel compounds that complement the traditional approach using beta-adrenergic blocking drugs, calcium antagonists, and long-acting nitrates. In the United States, ranolazine, a drug that inhibits late I_{Na} , was approved for patients with chronic angina that remain symptomatic on beta-blockers, calcium antagonists, or long-acting nitrates, on the basis of an acceptable safety profile and efficacy in several randomized placebo controlled studies. A slight increase in the QT interval is observed (< 10 ms on average) at the maximum approved dose of 1,000 mg twice daily. Therefore, an ECG should be acquired at baseline and during follow-up, and the drug should not be used in patients with QT prolongation or those who are on QT prolonging drugs unless longer term randomized outcome data demonstrates no excess risk. The MERLIN trial of non-ST-elevation acute coronary syndrome (NSTEMI/ACS) randomized 6,560 patients to assess the potential benefit of ranolazine in reducing the composite endpoint of cardiovascular death, myocardial infarction, and recurrent ischemia, with results expected in 2007. In Europe, ivabradine, a drug that inhibits the hyperpolarization-activated mixed sodium/potassium inward I_f current, which slows the rest and exercise heart rate, was approved in 2005. Ivabradine at a dose of 10 mg twice

daily has been shown to have similar efficacy to amlodipine 10 mg once daily or atenolol 100 mg once daily in alleviating chronic angina symptoms. In this review, several other novel investigational approaches are presented and patient selection considerations for the most recent approved drugs for chronic angina are discussed.

Key words: CARISA, enhanced external counterpulsation, ERICA, ivabradine, MARISA, MERLIN, nicorandil, ranolazine, rho, spinal cord stimulation, trimetazidine

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Introduction

Pharmacologic therapy (nitrates, beta-blockers, calcium antagonists), exercise conditioning, and coronary revascularization are treatments known to reduce angina frequency and nitroglycerin consumption, and increase the threshold at which demand-induced myocardial ischemic symptoms become manifest.¹ Several newer classes of drugs and alternative therapies have been introduced.^{2,3} On January 27, 2006, ranolazine was approved in the United States for the relief of angina in patients who remained symptomatic on beta-blockers, calcium antagonists, or nitrates.^{4–13} In other countries, ivabradine, nicorandil, and trimetazidine are treatments available for the symptomatic relief of angina.^{14–19} Other compounds have been investigated for potential treatment (e.g., rho-kinase and vasopeptidase inhibition) but are not commercially available.^{20,21} Nonpharmacological supplemental therapies, such as EECF and spinal cord stimulation, are also additions to the armamentarium. The focus of this review is to discuss some of the newer pharmacological therapies approved in the United States and Europe and their application as treatment options for chronic angina.

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TABLE 1 Selected trials of ranolazine in coronary artery disease

Study	Protocol design	Study results
Ran 080 ²⁷	4-week, double-blind, 3 group, 1-week period, crossover, placebo controlled trial of 158 patients with chronic angina randomized to Ran 400 mg t.i.d., atenolol 100 mg q.d. or placebo.	Both drugs significantly increased exercise-induced treadmill performance but ranolazine did not change exercise heart rate or blood pressure.
MARISA ⁴	4-week, double-blind, 4 group, crossover, placebo controlled trial of 191 patients with chronic angina on no background antianginal therapy randomized to Ran 500, 1,000, or 1,500 mg or placebo b.i.d.	Ranolazine significantly improved exercise-induced treadmill performance in a dose-dependent manner from 500–1,500 mg b.i.d. vs. placebo.
CARISA ⁵	12-week, double-blind, 3-group, placebo controlled trial of 823 patients with chronic angina on background therapy with either diltiazem 180 mg q.d., atenolol 50 mg q.d. or amlodipine 5 mg q.d.	Ranolazine significantly improved exercise-induced treadmill performance regardless of background therapy.
ERICA ⁹	6-week, double-blind, parallel-group, 3-phase, placebo controlled trial of 564 patients with chronic angina on amlodipine 10 mg q.d.	Ranolazine significantly reduced weekly number of angina attacks and nitroglycerin consumption.
MERLIN ²⁸	High-risk ACS patients randomized to IV ranolazine or placebo and transitioned to oral ranolazine or placebo with longer-term follow-up (>8 mo).	Primary endpoint is a composite of cardiovascular death, myocardial infarction, or recurrent ischemia. Study to be completed in late 2006.

Abbreviations: CARISA = Combination Assessment of Ranolazine in Stable Angina, ERICA = Efficacy of Ranolazine in Chronic Angina, MARISA = Monotherapy Assessment of Ranolazine in Stable Angina, MERLIN = Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Elevation, Ran = Ranolazine.

Ranolazine

Ranolazine ([(+)-N-(2,6-dimethylphenyl)-4-(2-hydroxy-3-(2-methoxyphenoxy)-propyl)-1-piperazine acetamide dihydrochloride]) is an active, piperazine derivative that was patented in 1986. RanexaTM (CV Therapeutics Inc., Palo Alto, CA) is the sustained-release ranolazine preparation recently approved.¹³ It has maximal plasma concentrations (C_{max}), typically seen 4–6 h after administration, and a peak/trough difference of 1.6-fold with 500–1,000 mg twice daily dosing. The Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) and subsequent CARISA and ERICA trials enrolled patients with chronic angina for at least 3 months.^{4,5,9} MARISA and CARISA required reproducible treadmill-induced angina and ST segment depression at low exercise workloads (<5 METS), whereas ERICA did not have a treadmill requirement (Table 1). Patients on drug therapy known to prolong the QT interval or with significant QTc prolongation at baseline were excluded. All three trials revealed an antianginal/antiischemic benefit in favor of ranolazine (Fig. 1). The CARISA trial showed a reduction in the mean number of weekly angina attacks and nitroglycerin use over the 12 weeks of treatment with ranolazine, a finding confirmed in the ERICA trial where a higher background dose of amlodipine was used (10 mg q.d.) and background long-acting nitrates were permitted. In a subset of CARISA analyses, treatment by background interaction terms were not significant for diabetic patients, men and women, older and younger subjects, and patients with a prior history of heart failure

(classified as per New York Heart Association (NYHA) class <III), an indication that the benefit in these subgroups were consistent with the main findings of the study.¹¹ Of the 746 MARISA and CARISA patients who received ranolazine 500–1000 mg b.i.d. over an average of 3 years in the Ranolazine Open Label Experience (ROLE), only 9.2% discontinued therapy in the first 2 years. There was a slightly greater discontinuation frequency in older subjects or patients with prior history of heart failure.¹² Overall mortality rate was 2.8% per patient year and the sudden cardiac death rate was 0.6% per patient year in this observational study. There are no reports of *torsades de pointes* in the ranolazine program to date. The most common adverse events reported with ranolazine are dizziness, nausea, asthenia, and constipation.^{4,5,11,13}

The mechanism of action of ranolazine is under investigation. Initially, it was thought to exert its therapeutic effects through partial inhibition of fatty acid oxidation. Subsequent studies demonstrate that it is not a pFOX inhibitor at therapeutic doses.²² Recent data indicate that ranolazine reduces calcium overload in the ischemic myocyte through inhibition of the late I_{Na} current^{6–8,13,23,24} (Fig. 2). Ranolazine is a relatively selective inhibitor for late I_{Na} , and in experimental preparations where the late I_{Na} is pathologically augmented, ranolazine prevented or reversed the induced mechanical dysfunction and also ameliorated abnormalities of ventricular repolarization. Excess intracellular sodium activates the sodium-calcium exchanger and can result in intracellular calcium overload via reverse transport

FIG. 1 In CARISA, exercise duration, time to onset of angina, and time to 1 mm ST segment depression significantly increased with each ranolazine dose compared to placebo. The differences were statistically significant for all exercise parameters at peak and at trough, with the exception of time to 1 mm ST segment depression. P-values for comparison of ranolazine vs. placebo. Least-square means and p-values from ANCOVA model with effects for treatment, baseline covariates, pooled site, and background therapy (n = 791).⁵ Reprinted from *J Cardiovasc Pharmacol Therapeut*, Vol. 9, Chaitman BR, Efficacy and safety of a metabolic modulator drug in chronic stable angina: Review of evidence from clinical trials, S47–S64, 2004, with permission.¹¹

of the sodium calcium exchanger. Impaired left ventricular relaxation and increased left ventricular end-diastolic pressure are early manifestations of myocardial ischemia, caused in part by calcium overload. In patients with chronic angina and demand-induced ischemia, ranolazine partially disrupts the consequences of cell hypoxia during transient myocardial ischemia by reducing excess late Na^+ influx, thereby reducing calcium overload and ultimately reducing the concomitant increase in left ventricular wall tension. Reduction in diastolic left ventricular wall tension would decrease myocardial oxygen requirements in marginally ischemic myocytes and has the potential to reduce vascular compression, allowing more coronary blood flow to the affected area. This relatively unique mechanism of action merits further study in cardiovascular conditions in which the late I_{Na} current is amplified, such as heart failure, acute coronary syndromes (currently being tested in the 6,560 patient MERLIN trial), certain types of cardiac sodium channel gene mutations, (e.g. long QT syndrome, type III) and cardiac arrhythmias.^{13,23–26} Other conditions, such as left ventricular diastolic dysfunction with preserved systolic function, in which animal experimental studies with ranolazine appear to show benefit, and skeletal muscle ischemia (intermittent claudication), should also be considered for study.

The starting dose of ranolazine is 500 mg b.i.d. and its maximum approved dose is 1,000 mg b.i.d. Ranolazine should not be used in patients with a prolonged QT interval or those on drugs known to prolong the QT. An ECG should be acquired at baseline and after treatment because ranolazine slightly prolongs the QT interval (on average <10 ms) unless outcome studies demonstrate the QT interval prolongation is not clinically significant. Ranolazine is primarily metabolized through

the CYP3A4 system and drugs known to inhibit this hepatic metabolic pathway, such as ketoconazole or other azole derivatives, macrolide antibiotics, protease inhibitors, diltiazem, or verapamil, increase ranolazine plasma concentrations and should not be used concomitantly. Ranolazine should not be used in patients with hepatic impairment. Ranolazine should be considered for patients with chronic angina that continue to be symptomatic on beta-blockers, calcium antagonists, or nitrates.

Trimetazidine

Trimetazidine has been shown in several randomized clinical trials to alleviate chronic angina^{16–19} (Table 2). Although the exact mechanism of action is controversial, it is believed to partially inhibit fatty acid oxidation, thereby improving myocardial substrate utilization by further shifting energy metabolism towards glucose utilization, a more efficient substrate when oxygen supply is limited. Trimetazidine has been used in Europe for at least two decades. The most common adverse events reported are nausea, vomiting, fatigue, and myalgia.

Sinus Node Inhibitor

Ivabradine selectively inhibits the hyperpolarization-activated, mixed sodium/potassium inward I_f current, a primary sinoatrial node (SAN) pacemaker current, thereby decreasing rest and exercise heart rate responsiveness.^{14,15} In a randomized trial of 360 patients with chronic angina, ivabradine improved work performance and time to onset of myocardial ischemia. In a subsequent comparator trial, ivabradine had similar efficacy to atenolol 100 mg q.d. in increasing exercise time in chronic angina and to amlodipine 10 mg q.d. in a

FIG. 2 Increases in intracellular sodium concentration ($[Na^+]_i$) in ischemic cardiac myocytes cause calcium (Ca^{2+}) overload via the Na^+-Ca^{2+} exchanger (NCX) leading to contractile dysfunction and cellular injury. A pathologically enhanced late Na^+ current (late I_{Na}) contributes to the $[Na^+]_i$ -dependent Ca^{2+} overload. Ranolazine, by decreasing the magnitude of the pathologically enhanced late I_{Na} , prevents or reduces Ca^{2+} overload and attenuates the accompanying deleterious consequences. Ranolazine does not alter the function of the normal heart in which late I_{Na} is a small current. Thus, ranolazine's action may be classified as cytoprotective. *Eur Heart J*, Vol. 6 (Supplement I), 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, 13–17, 2004, modified with permission from the European Society of Cardiology.⁸

different patient population. Visual disturbances, such as photopsia and stroboscopic effects were observed in 15% of subjects at a dose of 10 mg b.i.d. Ivabradine is currently being evaluated in a double-blind, placebo controlled trial of 10,000 patients with coronary disease and left ventricular dysfunction ($EF \leq 39\%$) to assess morbidity and mortality on top of optimal medical therapy, including beta-blockers. It is estimated to be completed by 2008.

TABLE 2 Selected trials of trimetazidine in chronic angina

TEMS ¹⁶	TMT 20 mg t.i.d. vs. propranolol 20 mg t.i.d. × 3 months in 149 men
South of France ¹⁷	TMT 20 mg t.i.d. or placebo added to diltiazem 60 mg t.i.d. × 6 months in 67 patients
TRIMPOL I ¹⁸	Nonrandomized: TMT added to background beta-blocker, calcium-channel blocker in 700 patients
TRIMPOL II ¹⁹	TMT 20 mg t.i.d. vs. Placebo added to metoprolol 50 mg b.i.d. × 3 months in 347 symptomatic patients with positive exercise treadmill test

Abbreviations: TEMS = Trimetazidine European Multicenter Study, TRIMPOL = TRIMetazidine in POLand.

Vasopeptidase Inhibition

Angiotensin converting enzyme inhibitors (ACEI) are cardioprotective in patients with coronary artery disease but ineffective in alleviating angina symptoms in normotensive or mildly hypertensive patients with preserved left ventricular function.²⁹ Bradykinin, atrial, and B-type natriuretic peptides have antiischemic properties and are released during myocardial ischemia. However, neutral endopeptidase 24.11 (NEP) inactivates vasodilatory and natriuretic peptides. Bradykinin is also degraded by angiotensin converting enzyme (ACE). Omapatrilat is a potent vasopeptidase inhibitor with selective and competitive inhibitory activity of ACE and NEP. We randomized 348 patients with chronic angina to omapatrilat or placebo in a double-blind placebo controlled multicenter trial.²¹ Omapatrilat increased total exercise capacity, time to onset of angina, and time to onset of ischemic ST segment depression at peak plasma concentrations and a significantly fewer number of patients reported angina during the test. Antianginal/antiischemic effects were markedly attenuated at trough plasma concentrations 24 h postdosing. Thus, broader vasopeptidase inhibition during ischemia may be a useful treatment to alleviate chronic angina symptoms, but it is still considered investigational because of a small incidence of angioedema.

Rho-Kinase Inhibitors

Rho is a family of small GTP-binding proteins that mediate intracellular signaling induced by activation of heterotrimeric G-protein-coupled receptors and growth receptors. In the cardiovascular system, Rho regulates vascular smooth muscle by modulating sensitivity to Ca^{++} . One of the Rho effectors is Rho-kinase (ROCK), which phosphorylates the myosin-binding subunit of myosin light chain (MLC) phosphatase and LIM kinase, ultimately regulating vascular smooth muscle contraction. In animal models of ischemic heart disease, inhibition of the MLC phosphorylation by Rho-kinase inhibition resulted in a decrease of vascular smooth muscle hypercontraction and reduction of ischemic ST segment depression. In a double-blind, placebo controlled, randomized clinical trial of 84 patients with chronic angina, fasudil, a ROCK inhibitor, was compared to placebo.²⁰ Both placebo and fasudil increased exercise time on treadmill testing compared to baseline, although

the difference between active drug (118 s increase) and placebo (86 s increase) was not statistically significant. Exercise time to onset of ischemic ST segment depression was significantly prolonged compared to placebo.

Nicorandil

Nicorandil, a hybrid compound of ATP-sensitive potassium channel opener and nitric oxide donor, reduces preload and afterload. In chronic angina studies, nicorandil has been shown to improve exercise capacity, but the results have not been consistent. In a small group of 83 patients with chronic angina, Thadani *et al.* reported no significant drug effect compared to placebo in exercise duration, time to onset of angina, or ischemic ST segment depression.³⁰ Dargie and colleagues randomized 5,126 higher-risk patients with chronic angina to nicorandil or placebo and reported a significant reduction in cardiac events after a mean 1.6 year follow-up.³¹ In another follow-up study of 368 patients with first STEMI undergoing PCI that received 12 mg of nicorandil IV or placebo, cardiovascular deaths and heart failure admissions were significantly reduced with nicorandil after a mean 2.4 years compared to placebo, and microvascular circulation was improved at the time of the procedure.³²

Patient Considerations

Chronic angina continues to be a morbid condition for many patients with coronary disease, adversely affecting both the quality and span of life. Relief of exertional angina symptoms can be obtained with beta-blockers, generally considered as initial therapy. Adequate beta blockade in the absence of undesirable side effects is optimal. For patients who remain symptomatic, or have contraindications to beta-blockers, the choice between calcium antagonists, long-acting nitrates, or a late INa inhibitor such as ranolazine (approved in the U.S.) can be considered depending on patient-specific characteristics. In patients with a low systolic blood pressure in whom additional vasodilation would be contraindicated, ranolazine would be a good choice since it has minimal effects on rest and exercise heart rate or blood pressure. In patients who require a blunted heart rate response to exercise but have contraindications to beta-blockers (e.g., asthma), ivabradine (not approved for use in the U.S.) or a calcium antagonist with negative chronotropic properties should be considered. Patients who require additional symptomatic relief might be candidates for trimetazidine or nicorandil (not approved for use in the U.S.). Ranolazine is contraindicated in patients on diltiazem and verapamil. Supplemental strategies such as EECp, spinal cord stimulation, or transmyocardial revascularization may also be beneficial in some patients.

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