Anti-anginal therapy in patients after acute coronary syndrome: evaluation of newer agents

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Abstract

Coronary heart disease (CAD) is the leading cause of death worldwide. Many patients who survive an acute myocardial infarction will experience recurrent angina which significantly impairs quality of life and in severe cases is associated with increased mortality. Angina occurs when there is a mismatch between coronary supply and demand. Traditional agents including β-blockers, calcium-channel blockers and nitrates exert their effect by reducing the hemodynamic components of myocardial oxygen demand such as heart rate, blood pressure and preload. After several decades without new therapies in our pharmacologic armamentarium, several promising new agents have undergone clinical evaluation with promising results. Some of these novel agents exert their anti-anginal effects through reduction in traditional hemodynamic parameters but others target novel steps in the ischemic pathway. This review examines the pharmacologic management of angina in patients after acute coronary syndrome (ACS) with a focus on novel agents.

Key words: acute coronary syndrome, angina, nicorandil, ranolazine, trimetazidine.

Introduction

Coronary heart disease (CAD) is the leading cause of death worldwide and its incidence is rapidly rising as the epidemic of obesity and diabetes spreads globally [1]. It is estimated that CAD is responsible for over 20% of deaths in the United States [2]. Most often, atherosclerosis progresses gradually and patients experience chronic, exertional angina which results a dramatic reduction in quality of life and, in severe cases, is associated with increased mortality [3, 4]. In some, a vulnerable atherosclerotic plaque ruptures, suddenly occluding a coronary artery and resulting in an acute coronary syndrome (ACS). Among those who survive an acute myocardial infarction, nearly 20% will have recurrent symptoms within one year [5].

To confront the major challenge that CAD poses to the health care the system the American College of Cardiology and the American Heart Association have prioritized the dual goals of preventing major cardiovascular events, thereby improving survival, and enhancing quality of life by reducing ischemic symptoms [6]. Pharmacologic and lifestyle modifications for all patients with CAD should encompass aggressive reduction of atherosclerotic risk factors such as optimization of blood pressure and lipid parameters. This review will specifically examine the pharmacologic management of angina in patients after ACS, focusing on novel agents.

Traditional anti-anginal therapies

Angina is the hallmark ischemic manifestation of CAD that occurs when there is a mismatch between coronary supply and demand. Both traditional and novel pharmacologic anti-anginal therapy attempt to ameliorate this imbalance between myocardial oxygen supply and demand.

The three classes comprising traditional anti-anginal therapies are β-blockers, calcium-channel blockers and nitrates. All three exert their effect by reducing the hemodynamic components of myocardial oxygen demand such as heart rate, blood pressure and preload. All three have been shown to be effective in decreasing angina and increasing ischemic threshold with exercise with no clear superiority of single class or agent with respect to relief of symptoms [7-9].

β-Blockers

β-Blockers should be considered first-line anti-anginal therapy due to their proven benefit in reducing both mortality and recurrent myocardial infarction in patients with a previous myocardial infarction. All β-blockers reduce myocardial oxygen demand by blunting the effects of catecholamines. This leads to a reduction in heart rate (exercise and rest), systolic blood pressure and contractility. Lower heart rates also have the benefit of prolonging diastolic filling time, enhancing coronary blood flow thereby increasing supply. In addition to ameliorating angina, β-blockers have important anti-arrhythmic activity. β-Blockers are started at a low initial dose and are gradually titrated to achieve a resting heart rate of 55 to 60 beats per minute or an exercise heart rate that is 75% of the ischemic threshold [2]. Caution is required in patients with severe left ventricular dysfunction due to the negative inotropic effects.

The COMMIT trial investigated the benefit of early intravenous and oral β-blockade in over 45,000 patients presenting with acute mycocardial infarction [10]. Early β-blocker therapy reduced the risk of reinfarction (OR 0.82, 95% CI 0.72-0.92, $p = 0.001$) and ventricular fibrillation (OR 0.83, 95% CI 0.75-0.93, $p = 0.001$) compared to placebo but increased in the risk of cardiogenic shock (OR 1.30, 95% CI 1.19-1.41, $p < 0.00001$). These results highlight the important benefits of β-blockade but caution that therapy should be initiated in hemodynamically stable patients.

Calcium-channel blockers

Calcium-channel blockers reduce calcium influx into myocardial and smooth muscle cells by blocking the L-type calcium channel. There are two types of calcium channel blockers, dihydropyridines (amlodipine, nifedipine, felodipine, nicardipine) and non-dihydropyridines (verapamil, diltiazem). Both types exert their anti-anginal properties by enhancing vascular smooth muscle relaxation resulting in a reduction in blood pressure. Because of their properties on vascular smooth muscle, calcium-channel blockers are particularly effective when there is a suspected vasospastic anginal component. Non-dihydropyridines also slow heart rate through effects on cardiac nodal tissue. Because of this differential affect, dihydropyridines should be used in combination with β-blockers to prevent reflex tachycardia. Due to their more potent negative inotropic effects, non-dihydropyridines should be used with caution in patients with severe left ventricular dysfunction because of reports of increased mortality [7].

Calcium-channel blocker therapy in the post-myocardial population was studied in an INVEST substudy which compared verapamil (sustained release) to atenolol based strategies [11]. Verapamil was equivalent to atenolol for blood pressure control and prevention of cardiovascular events, with a trend toward lower incidence of angina (12.0 vs. 14.3%, adjusted $p = 0.07$).

Nitrates

Nitrates act by stimulating cyclic guanosine monophosphate (cGMP) leading to smooth muscle relaxation. Although nitrates cause vasodilation of coronary and peripheral arterial beds, their principal effect is mediated by potent venodilation which reduces ventricular preload thereby reducing myocardial oxygen demand. Nitrates, both alone and in combination with other anti-anginal agents, have demonstrated efficacy in reducing symptoms, improving exercise duration and increasing ischemic exercise thresholds [7, 8]. They are particularly effective in patients with ischemia and systolic heart failure. Nitrates can be given in sublingual, oral and transdermal preparations. Long-acting nitrates are available and offer improved compliance but care must be given to ensure a 12 h "nitrate-free" period to avoid the development of tolerance. Patients taking nitrates should be warned not to take concomitant phosphodiesterase-5 inhibitors (sildenefil, tadalafil, vardenafil) within a 24 h period due to the danger of precipitating significant hypotension.

Novel pharmacologic agents

After several decades without any new therapies becoming available for the treatment of angina there are now several new promising agents that have undergone clinical evaluation. Several of these agents (Table I) exert their anti-anginal effects through reduction in the hemodynamic parameters (heart rate, preload, afterload) but others interact

Table I. Novel agents and their proposed mechanism of action

Agent	Mechanism of action
Fasudil	Inhibits Rho-kinase leading to vascular smooth muscle relaxation and vasodilation
Trimetazidine	Improves myocardial metabolism during ischemia by inhibiting partial-fatty acid oxidation
Ivabradine	Reduces heart rate by inhibiting the If channel in the sinoatrial node
Nicorandil	ATP-sensitive potassium channel opener and nitric oxide donor that promotes peripheral and coronary vasodilation
Ranolazine	Inhibits the late sodium current (late I_{NA}), preventing intracellular calcium overload and impaired myocyte relaxation

with novel targets in the ischemic pathway that may not only complement traditional therapies but also treat dynamic components of angina such as microvascular disease and vasospasm.

Nicorandil

Nicorandil is an adenosine triphosphate-sensitive potassium channel (KATP) opener and nitric oxide donor that increases coronary blood flow and reduces preload and afterload through dilation of peripheral and coronary resistance arterioles as well as systemic veins and epicardial coronary arteries [12-15].

In early clinical studies it was shown to be as safe and as effective as traditional anti-anginal therapies [16, 17]. Nicorandil was evaluated in the large multicenter Impact of Nicorandil in Angina (IONA) trial which enrolled 5126 patients with stable angina who were randomized to 20 mg twice daily or placebo [18]. Nicroandil reduced the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, or unplanned hospital admission for angina by 17% (13.1 vs. 15.5%, HR 0.83, 95% CI 0.72-0.97, $p = 0.014$) (Figure 1), though there was no difference in the rate of cardiovascular death alone over the 1.6 year follow-up.

In two small studies of patients with ischemic cardiomyopathy and patients presenting with their first acute myocardial infarction, nicorandil improved cardiac sympathetic nerve activity and left ventricular remodeling as measured by nuclear and echocardiographic parameters compared to conventional therapy [19, 20]. A 5 year follow-up study in patients with ST-segment elevation myocardial infarction who were given a single intravenous administration of nicorandil prior to reperfusion demonstrated improvements in clinical outcomes, experiencing significantly fewer cardiovascular deaths or hospital admissions for congestive heart failure compared to placebo (HR 0.39, 95% CI 0.20 to 0.76, $p = 0.0058$) [21, 22].

Another large multicenter trial (J-WIND), enrolled patients presenting with their first episode of acute ST-segment elevation myocardial infarction undergoing reperfusion into two single-blind trials

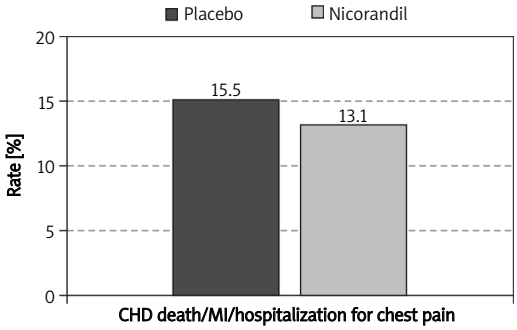

Figure 1. Reduction of cardiovascular events in patients with stable angina in the Impact of Nicorandil in Angina (IONA) trial [30]
CHD – coronary heart disease, MI – myocardial infarction, OR – odds ratio

investigating human atrial natriuretic peptide and nicorandil as adjunct therapies [23]. There were 276 patients assigned to the intravenous nicorandil group (24 h infusion) and 269 patients who received placebo. Medium follow-up was 2.5 years. Nirorandil did not reduce infarct size (estimated as the area under the concentration versus time curve for creatinine kinase) or improve left ventricular ejection fraction (measured by angiography) compared to placebo (Figure 2).

Ranolazine

Ranolazine, a piperazine derivative, was approved by the FDA in 2006 for the treatment of patients with chronic stable angina. Although ranolazine does inhibit partial-fatty acid oxidation at very high concentrations, similar to trimetazidine, it appears to mediate its physiologic effects at the dosages prescribed by inhibiting the late phase of the sodium current (late I_{NA}). In normal physiologic conditions, there is early activation of the sodium channel during cell depolarization (peak I_{NA}) with a prolonged inactivation state. In pathologic conditions, such as ischemia, some of the sodium channels fail to close leading to an increase in late sodium current. Elevated intracellular sodium concentrations lead to an increase in intracellular calcium through the sodium-calcium exchanger, which has several deleterious downstream effects.

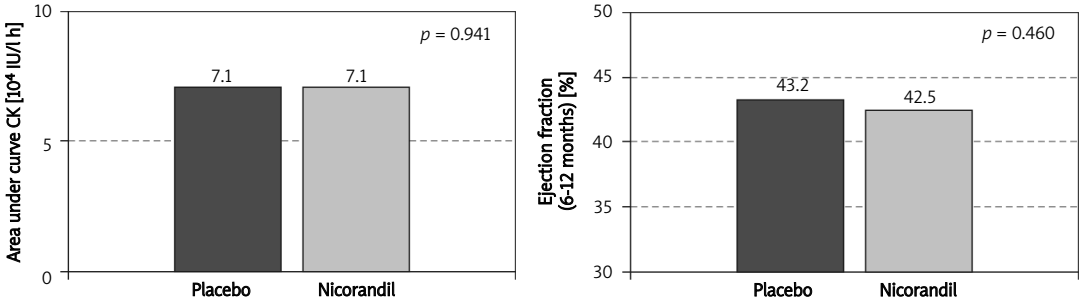

Figure 2. Effect of nicorandil on infarct size and left ventricular ejection fraction in patients presenting with acute ST-segment elevation myocardial infarction in the JWIND trial [31]
CK – creatine kinase, h – hour, IU – international units

Myocyte relaxation is impaired, increasing end-diastolic pressure which diminishes tissue perfusion and contractility.

There have been three randomized, controlled trials examining extended-release ranolazine in patients with chronic angina. The Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) trial was designed to determine the dose-response relationship of ranolazine on symptom-limited exercise duration on a modified Bruce protocol treadmill test [24]. The results demonstrated that ranolazine monotherapy at all three doses studied was safe and increased exercise performance independent of heart rate and blood pressure. The efficacy of ranolazine in patients with symptomatic chronic angina taking a combination of concurrent atenolol, amlodipine or diltiazem was confirmed in the Combination Assessment of Ranolazine in Stable Angina (CARISA) trial [25]. Compared to placebo, ranolazine increased total exercise duration, and reduced anginal episodes and nitroglycerin use. The third trial, Efficacy of Ranolazine in Chronic Angina (ERICA), randomized 565 patients with symptomatic angina to ranolazine (1000 mg twice daily) or placebo and followed them for 6 weeks [26]. All patients were on maximum dose of amlodipine and half of the patients took long-acting nitrates. Ranolazine significantly reduced angina and nitroglycerin use. These anti-ischemic effects of ranolazine are achieved without a clinically significant effect on heart rate or blood pressure. Therefore, ranolazine may have a particular role in complementing traditional anti-anginal therapy when limited by heart rate or blood pressure.

The efficacy of ranolazine in the setting of unstable angina and non-ST elevation MI was investigated in the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndromes (MERLIN-TIMI 36) trial [27]. Six thousand five hundred and sixty patients were randomized to ranolazine (1000 mg twice daily) vs. placebo and were followed for a median time of approximately one-year. Ranolazine did not reduce the rate of the composite primary endpoint of cardiovascular death, myocardial infarction or recurrent ischemia (21.8 vs. 23.5%, HR 0.92, 95% CI 0.83-1.02, $p = 0.11$) but did demonstrate a 13% reduction in the risk of recurrent ischemia, in particular worsening angina (HR 0.87, 95% CI 0.76-0.99, $p = 0.03$) (Figure 3). Therefore, on the basis of these results, ranolazine does not have a role for routine use in the acute management of ACS. However, ranolazine is effective in reducing recurrent symptoms in those with established ischemic heart disease and a recent ACS.

Interestingly, although ranolazine prolongs the QTc interval on average by 2-6 ms and monitoring the QTc is recommended, in this high risk population with ischemic heart disease ranolazine reduced in the incidence of arrhythmias detected on 7 day Holter monitoring in the MERLIN-TIMI 36 trial [28]. Patients randomized to ranolazine had fewer episodes of ventricular tachycardia (5.3 vs. 8.3%, $p < 0.001$), supraventricular tachycardia (44.7 vs. 55.0%, $p < 0.001$), or new-onset atrial fibrillation (1.7 vs. 2.4%, $p = 0.08$). These data suggest that ranolazine may have a possible anti-arrhythmic effect warranting additional study.

Trimetazidine

Trimetazidine is thought to improve myocardial metabolism during ischemia by inhibiting partial-fatty acid oxidation and enhancing utilization of glucose dependent oxidation which more efficiently generates ATP in a low oxygen environment [29]. In clinical trials of patients with angina it has been shown to reduce weekly symptomatic episodes and prolong the time until ST depression on exercise testing, even in patients on maximal traditional anti-anginal agents [30, 31].

Trimetazidine was studied in patients presenting with acute myocardial infarction in the EMIP-FR trial [32]. Over 19,000 subjects were randomized to bolus intravenous trimetazidine followed by 48 h infusion or placebo. The overall results demonstrated no difference in short or long term mortality although there were opposing trends when the results were stratified by whether thrombolysis was admini-

stered. Thrombolysed patients showed a tendency towards more short-term deaths with trimetazidine compared to placebo (11.3 vs. 10.5%, $p = 0.15$) but non-thrombolysed patients demonstrated a trend towards a benefit (14.0 vs. 15.1%, $p = 0.14$).

Ivabradine

Ivabradine reduces both rest and exercise heart rate without negative inotropic effects by selectively inhibiting the If ion channel in the sinoatrial node. In several studies in patients with stable angina, ivabradine demonstrated equivalence to both atenolol and amlodipine in improving exercise tolerance and time to development of ischemia during exercise [33, 34]. In the BEAUTIFUL study, which enrolled patients with stable coronary artery disease and systolic dysfunction, treatment with ivabradine did not improve the primary composite outcome of cardiovascular death or heart failure hospitalization but did reduce the incidence of hospitalization for myocardial infarction and coronary revascularization in a prespecified subgroup of patients with heart rates ≥ 70 bpm [35].

Fasudil

Fasudil inhibits Rho-kinase leading to vascular smooth muscle relaxation and vasodilation. Rho-kinase, an effector molecule of the small GTP-binding protein Rho, not only plays a role in vasomotion of arteries but is thought to upregulate various pathways involved in inflammation, oxidative stress, thrombus formation and fibrosis [36]. Intracoronary administration of fasudil has been shown to be a more effective vasodilator than nitroglycerin at sites of coronary stenosis in patients with stable angina [37]. In a double-blind, placebo-controlled, phase 2 trial in patients with stable angina, oral fasudil significantly increased the ischemic threshold during exercise with a trend toward increased exercise duration but did not reduce the frequency of anginal episodes [38]. Fasudil has not been studied in patients with ACS.

Conclusions

The recurrence of angina after an acute coronary syndrome is common and adversely impacts quality of life. Therefore, management of patients who are post-ACS includes both disease-modifying therapy to reduce the risk of recurrence of MI or cardiac death. The focus appropriately should be on aggressive control of cardiac risk factors with both disease modifying pharmacologic agents and lifestyle interventions. However, amelioration of recurrent symptoms has an important impact on quality of life [39]. The optimal selection of agents should be influenced by individual patient characteristics. β-Blockers are preferred as the first-line agent unless contraindicated because of their proven mortality benefit in patients with prior MI. Newer agents, such as ranolazine, that act via novel mechanisms may be used to complement β-blockers and other traditional anti-anginal agents, particularly when limited by heart rate, blood pressure, or unacceptable side effects.

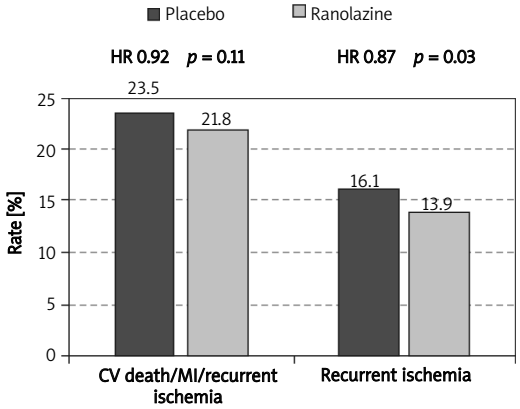

Figure 3. Effect of ranolazine on cardiovascular outcomes in patients presenting with non-ST-elevation myocardial infarction in the MERLIN-TIMI 36 trial [35]
CV – cardiovascular, HR – hazard ration, MI – myocardial infarction

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