ABSTRACT

Despite treatment with traditional pharmacotherapy and/or revascularization, angina remains a significant health problem for many patients with ischemic heart disease. Novel agents that manipulate cardiac metabolism in the ischemic state to provide relief from anginal symptoms may prove beneficial to many patients with persistent angina despite traditional treatment. Recent clinical data using novel pharmacologic compounds to optimize metabolism in cardiac ischemia as well as clinical implications of these agents are reviewed. Ranolazine and trimetazidine, 2 orally active partial free fatty acid oxidation inhibitors, have demonstrated angina relief independent of hemodynamic effects as monotherapy or in combination with traditional antianginal medication. Ranolazine is currently under review by the US Food and Drug Administration for approval in the United States. Trimetazidine is approved in more than 80 countries but is not likely to receive approval in the United States until its effects on the QT interval, toxicity at higher doses, and a randomized dose-response study are formally evaluated. Although not practical for chronic administration in the angina patient, beneficial effects of continuous infusion with glucose, insulin, and potassium in patients post acute myocardial infarction (AMI) may provide important insight into the development of new antianginal therapy. Glucagon-like peptide-1 has demonstrated beneficial global and regional ventricular function in a pilot study of patients after successful reperfusion after AMI. The anti-ischemic agent ivabradine is an indirect metabolic modulator and has demonstrated a reduction in major coronary events in patients with stable angina. This cardioprotective benefit observed with ivabradine may be associated with an improvement in fibrinolytic capacity. To date clinical experience with this novel class of agents is limited in the United States. However, controlled clinical studies are encouraging regarding the future use of these agents as a novel strategy for the management of coronary artery disease. Finally, further data are needed to determine if these novel therapies will be able to fill the gap in angina relief in patients who remain refractory with traditional pharmacotherapy commonly coupled with revascularization.

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core than 64 million Americans have one or more types of cardiovascular disease including chronic angina in 6.8 million of these patients. Modification of risk factors is a requirement for all patients with coronary artery disease and usually includes pharmacological therapy and/or a revascularization procedure to improve survival and to improve the patient’s quality of life. Despite numerous treatment options, chronic angina remains an important unresolved health problem. Neither antianginal drug therapy nor revascularization guarantees the cessation of angina. On the contrary, recent evidence suggests that angina symptoms persist in 88% of patients on medical management and in 56% of chronic angina patients who

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have undergone revascularization procedures. Collectively, these data support the need for alternative treatment strategies to relieve symptoms of angina.

Various traditional drug therapies have been used to treat chronic stable angina including antiplatelet agents, beta blockers, angiotensin-converting enzyme inhibitors, lipid-lowering agents, calcium channel blockers, and nitroglycerin. These agents share a similar mechanism of action that involves the reduction of myocardial oxygen demand via an increase in coronary blood flow and a reduction in heart rate, cardiac contractility, arterial blood pressure, and afterload on the left ventricle. Another treatment option for the angina patient involves the administration of novel therapies that manipulate cardiac metabolism in the ischemic state to provide relief from anginal symptoms. Recent clinical data of pharmacologic interventions used to optimize cardiac metabolism in cardiac ischemia are beginning to demonstrate beneficial effects. These data and their clinical implications are reviewed for the following agents: ranolazine, trimetazidine, glucose-insulin-potassium (GIK), glucagon-like peptide-1 (GLP-1), and ivabradine.

**PARTIAL FREE FATTY ACID OXIDATION INHIBITORS**

Two partial free fatty acid oxidation inhibitors, ranolazine and trimetazidine, have been shown to provide beneficial effects on the ischemic heart without altering central hemodynamics or baseline contractile parameters as observed with traditional antianginal drug therapy. Both ranolazine and trimetazidine are orally active piperazine derivatives.

**RANOLAZINE**

Ranolazine is an investigational agent currently under review at the US Food and Drug Administration (FDA) for approval in the United States. In vivo and in vitro studies conducted in cardiac preparations from a variety of animal species as measured by different indices of ischemic damage have demonstrated the efficacy of ranolazine. Sustained-release (SR) formulations of ranolazine have demonstrated efficacy and safety in stable angina patients when given as monotherapy and in combination with traditional therapy.

The first trial of monotherapy with SR ranolazine in patients with chronic angina was the Monotherapy Assessment of Ranolazine In Stable Angina (MARISA) study. The primary objective of this multinational study was to evaluate the efficacy of twice-daily SR ranolazine 750 mg (n = 279) or 1000 mg (n = 275) compared with placebo (n = 269) on treadmill exercise duration at trough ranolazine levels. Of the 823 patients randomized, 43% were taking atenolol, 31.1% amlodipine, and 25.9% diltiazem at enrollment. Compared with placebo, both doses of SR ranolazine demonstrated an increase in treadmill exercise duration at both trough \( (P = .03) \) and peak \( (P < .02) \), an effect that was sustained throughout 12 weeks of therapy. In addition, SR ranolazine was associated with a significant reduction in the number of anginal episodes and frequency of nitroglycerin consumption compared with placebo \( (P = .02) \). Ranolazine did not exert any clinically meaningful effects on standing or end-exercise heart rates or blood pressures. The most common dose-related side
effects of ranolazine were constipation, dizziness, nausea, and asthenia. Of the 750 patients who took ranolazine during the CARISA study or during the open-label follow-up period, survival rates were 98.4% at 1 year and 96% at 2 years.

Final approval of ranolazine for the management of acute and chronic coronary artery disease is dependent on the approval-enabling study agreed upon between the company supplying the drug and the FDA. Here, via the FDA special protocol assessment program, ranolazine is currently being studied in non-ST elevation acute coronary syndrome in the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndromes (MERLIN) study.12

**TRIMETAZIDINE**

Trimetazidine has demonstrated antianginal properties via manipulation of cardiac metabolism in animal models and in humans.13-17 Trimetazidine is approved in over 80 countries; however, a randomized dose-response study as well as an evaluation of toxicity at higher doses and effects on QT interval need to be explored prior to this agent being considered for approval in the United States.

A meta-analysis of 12 double-blind, randomized, controlled clinical trials of trimetazidine in the treatment of stable angina was published in 2003.18 This analysis of studies conducted from 1986 to 2001 included patients who were treated with trimetazidine for at least 2 weeks and included control with placebo or conventional antianginal therapy. Trimetazidine was associated with significant reductions in the number of weekly angina attacks, improved time to 1-mm segment depression, and total work at peak exercise (P<.05). A trend towards improvement with trimetazidine was observed in exercise duration at peak exercise (P =.09). Tolerability of trimetazidine was mentioned in only 8 of these 12 studies, and was not thoroughly evaluated in most of these trials. The most frequently reported adverse events were related to the gastrointestinal tract (such as nausea, epigastric pain, gastric burning, constipation, and anorexia), headaches, and muscular cramps. Overall, this meta-analysis showed that trimetazidine is an effective antianginal agent when used alone or in combination with traditional hemodynamic agents.

**Table. Trimetazidine Plus Low-Dose Diltiazem for the Treatment of Stable Angina**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>90 mg Diltiazem + 60 mg Trimetazidine per Day (n = 25)</th>
<th>90 mg Diltiazem + Placebo per Day (n = 25)</th>
<th>Difference in Response % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anginal attacks per week</td>
<td>17 (68)</td>
<td>3 (12)</td>
<td>74 (58 - 84)</td>
</tr>
<tr>
<td>Glyceryl trinitrate tablets per week</td>
<td>15 (60)</td>
<td>6 (24)</td>
<td>62 (36 - 88)</td>
</tr>
<tr>
<td>Exercise time (sec)</td>
<td></td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>At onset of angina*</td>
<td>2 (20)</td>
<td>2 (20)</td>
<td>57 (32 - 82)</td>
</tr>
<tr>
<td>At 1-mm ST-segment depression</td>
<td>13 (52)</td>
<td>5 (20)</td>
<td>22 (7 - 37)</td>
</tr>
<tr>
<td>At peak exercise</td>
<td>5 (20)</td>
<td>4 (16)</td>
<td>5 (20 - 15)</td>
</tr>
<tr>
<td>Maximum work at peak exercise (mets)†</td>
<td>3 (12)</td>
<td>2 (8)</td>
<td>3 (12 - 18)</td>
</tr>
<tr>
<td>Maximum ST-segment depression at peak exercise (mm)</td>
<td>2 (8)</td>
<td>5 (20)</td>
<td>6.7 (12 - 81)</td>
</tr>
</tbody>
</table>

*10 patients in each group developed angina during exercise at both baseline and after treatment at day 28.
†Metabolic equivalents
CI = confidence interval; NS = not significant.
A randomized, double-blind, placebo-controlled study recently evaluated the efficacy and tolerability of trimetazidine in combination with diltiazem in stable angina. Patients were to receive low-dose diltiazem (90 mg once daily) and sublingual glyceryl trinitrate and were randomized to trimetazidine 60 mg once daily (n = 25) or placebo (n = 25) for 28 days. The primary objective of this study was change in time to 1-mm ST-segment depression. Response to treatment was defined as a minimum of a 50% improvement from baseline in the primary outcome, other exercise test measurements and angina, or an increase in the Duke treadmill score. Significantly more patients showed an improvement in anginal attacks per week, intake of glyceryl nitrate tablets per week, and exercise time at 1-mm ST-segment depression with trimetazidine plus diltiazem compared with diltiazem alone ($P \leq .0225$) (Table). No patients withdrew from the study due to side effects and the only adverse events reported were constipation in 2 patients treated with placebo.

Six months of therapy with a modified-release (MR) formulation of trimetazidine dosed twice daily has been evaluated in patients with stable angina pectoris. Patients in this multinational, randomized, double-blind, placebo-controlled study received atenolol 50 mg per day and MR trimetazidine 35 mg (n = 117) or placebo (n = 106) for 6 months following a 3-week run-in period of atenolol 50 mg once daily and placebo. Primary efficacy was based upon change in time to 1-mm ST-segment depression. Time to 1-mm ST-segment depression was increased significantly with trimetazidine compared with placebo ($P = .005$). Rates of adverse events were similar and no differences in corrected QT intervals were observed between treatment groups.

Hence, although the clinical experience with trimetazidine has been both promising and extensive in other parts of the world, we are unaware of efforts to present this drug to the FDA for evaluation for use in the United States. This may, in part, be due to the limited published data on dose response, safety, and pharmacokinetic properties. Conceptually, however, the clinical benefit and widespread use of trimetazidine in other countries may be encouraging for ranolazine in the United States once the FDA is satisfied with its safety and efficacy profile.

**GIK**

Continuous infusion of GIK has been evaluated in patients presenting within 24 hours after experiencing an acute myocardial infarction (AMI). Promising results of the Estudios Cardiológicos Latinoamérica (ECLA) pilot study with metabolic modulation with GIK in the AMI setting led to a full-scale clinical trial for confirmation of the benefits of GIK within the first few hours post AMI. Additionally, favorable results have been observed with open-label GIK as adjuvant therapy to percutaneous transluminal angioplasty in AMI patients without signs of heart failure. A large randomized trial is under way to confirm these results. These studies were conducted in the post-AMI setting and chronic administration of GIK for patients with chronic angina is not practical. However, the beneficial effects of GIK serve as a “proof of concept” that metabolic modulation may yet find a niche in the pharmacologic armamentarium of health providers in the management of coronary artery disease.

**GLP-1**

GLP-1 is a naturally occurring incretin with insulinotropic and insulinomimetic properties. Together these stimulate glucose uptake without the risk of hypoglycemia, thereby reducing the need for concomitant glucose infusion. This preparation is a recombinant that can be infused intravenously or administered more chronically as a subcutaneous preparation.

Effects on global and regional ventricular function of a continuous 72-hour infusion of GLP-1 were evaluated in a single-center nonrandomized pilot study. Ten patients with Killip class III to IV after successful reperfusion in AMI were enrolled in this study and were compared with a group of control patients (n = 11) receiving comparable medical and interventional therapy but not GLP-1. Global left ventricular ejection fraction was significantly improved with GLP-1 ($P <.01$) but not in the control group. In addition, GLP-1 was associated with regional functional recovery in the peri-infarct zone. Beneficial effects of GLP-1 were independent from hemodynamic effects and were observed in patients with or without concurrent diabetes. GLP-1 was well tolerated and adverse events were reversible. Albeit very preliminary, these data suggest that this agent, once studied to a greater extent, may become useful in the management of the acute coronary syndrome.

**IVABRADINE**

Ivabradine is an indirect metabolic modulator in that it diminishes cardiac energy demand as opposed...
to modulating the supply of oxygen to the heart muscle. The effects of ivabradine on time to 1-mm ST-segment depression and time to limiting angina during standardized bicycle exercise tolerance tests (ETT) were investigated in a randomized, double-blind, placebo-controlled, multinational, parallel-arm trial. Three hundred sixty patients were randomized to receive ivabradine (2.5, 5, or 10 mg twice daily) or placebo for 2 weeks followed by a voluntary 2- to 3-month open-label extension phase of ivabradine 10 mg twice daily. The primary endpoint was changes in time to 1-mm horizontal or downsloping ST-segment depression .08 or more seconds after the J point and time to limiting angina during ETT at trough. During the double-blind, dose-ranging phase, all doses of ivabradine were associated with an increase in time to 1-mm ST-segment depression during ETT and this increase was significantly greater than with placebo for the 5- and 10-mg doses \((P = .005)\). Times to the onset of angina and to limiting angina increased with all doses of ivabradine and reached significance with the 10-mg group. These beneficial effects of ivabradine were maintained in the open-label phase and patients who originally received placebo experienced a reduction in ischemia and angina with open-label ivabradine (Figure). Patients treated with ivabradine experienced visual symptoms in a dose-dependent manner; however, all visual symptoms spontaneously resolved during or after drug discontinuation. Cessation of ivabradine does not seem to be associated with a rebound phenomenon as no serious cardiac events were reported after discontinuation of ivabradine treatment. Ivabradine appears to be early in its drug development cycle and we will watch its progress with interest.

**CONCLUSIONS**

As evidenced by the robust quantity of recent clinical data on various novel antianginal therapies, this is indeed a promising time for practitioners caring for patients with chronic angina. Many patients continue to suffer from anginal symptoms despite treatment with traditional antianginal medication. Revascularization offers improvement for sufferers of chronic angina; however, about one fourth of patients able to undergo revascularization are not free from angina after 1 year. Clinical experience with many of these metabolic modulatory agents is encouraging, however, further data are needed to determine if these novel therapies will be able to fill the gap in anginal relief in many patients who remain refractory with traditional pharmacotherapy commonly coupled with revascularization.

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**Figure. Effect of Ivabradine on 1-mm ST-Segment Depression and Time to Limiting Angina**

REFERENCES


