INTRODUCTION

In India, due to increasing CAD risk factors, the prevalence of CAD continues to increase. As per the guidelines, the aim of CAD treatment should be improving prognosis by preventing myocardial infarction and death along with minimizing or abolishing symptoms.

Therapeutic options include pharmacologic therapy, percutaneous coronary interventions (PCI), coronary bypass surgery (CABG) and newer therapies including enhanced external counterpulsation and investigational gene therapy. The number of patients with CAD that is refractory to these therapies also continues to increase. So, it remains important to develop new medical treatments of ischemic heart disease (IHD).

Current management paradigms focus on medications directed toward optimizing cardiac hemodynamic effects. The optimal hemodynamic treatment, including combination of 3 conventional drugs is not always effective in stable angina patients. Moreover studies also prove that there is no synergistic benefit noted when conventional drugs are combined in stable angina. Therefore in addition to hemodynamic treatments, a novel group of agents that work via other mechanisms are available for the treatment of myocardial ischemia. These agents improve cardiac metabolism and cardiac energy availability and are termed metabolic modulators. They include trimetazidine, ranolazine, dichloroacetate, L-carnitine, etomoxir and D-ribose.

The metabolic approach to treating IHD is not new; 94 years ago it was observed that chest pain could be relieved by administration of sugar to patients with heart disease. In late 1960s and 1970s, the use of metabolic therapies for treating ischemic myocardium received a great attention following the observation that an infusion of glucose, insulin and potassium (GIK) reduced ventricular dysrhythmias and increased survival following a myocardial infarction (MI). Oliver and co-workers developed the concept that suppression of circulating plasma nonesterified fatty acids, and thus myocardial fatty acids uptake and oxidation, reduced ischemic damage and ventricular dysrhythmias during acute MI or exercise induced angina. It has been shown that direct inhibition of fatty acid transport into the mitochondria with oxefine increase glucose oxidation and decreases lactate production, resulting in symptom relief in patients with stable angina.

These metabolic changes can be monitored by single photoemission computed monography (SPECT) imaging.

METABOLIC MODULATION IN IHD

Patients who have ongoing anginal symptoms despite receiving optimal standard therapy should be considered for the alternative treatment strategy: metabolic modulation. The various metabolic antianginal drugs are reviewed in the following sections.

GLUCOSE INSULIN POTASSIUM (GIK)

Acute administration of insulin, alone (in hyperglycemic diabetics) or together with glucose and potassium, has been widely postulated to induce potential beneficial effects in acute myocardial ischemia by altering myocardial metabolism. The use of insulin in the presence of diabetes has been well established since the DIGAMI trial, which demonstrated a
significant long-term mortality benefit in diabetic patients treated with insulin following myocardial infarction (MI)\(^1\). Though it is beyond the scope of this review to present all the evidence for the utility of GIK in non-diabetics during acute myocardial infarction, we have summarized some of the key studies investigating the utility of GIK in the acute ischemic setting.

A meta-analysis by Fath-Ordoubadi and Beatt\(^2\) suggests that GIK infusion improves outcome postmyocardial infarction even in patients without diabetes mellitus. The observed improvements in mortality following GIK infusion post-MI appear to hold true even in the context of contemporary treatment with thrombolysis or percutaneous coronary intervention, as demonstrated by the ECLA study\(^3\).

Two studies conducted in the post-MI setting\(^4,5\), however, failed to demonstrate a significant short-term mortality benefit with GIK therapy. A Dutch study conducted in association with primary percutaneous coronary intervention suggested, on post hoc analysis, a reduction in mortality confined to patients without heart failure at presentation\(^4\). While, in theory, this might reflect greater early access of GIK to the ischemic zone (via collaterals), these results should be confirmed on a prospective basis. The negative Polish study\(^5\) used lower doses of GIK than other positive studies and a lower-risk cohort. It has therefore been suggested that higher-risk patients may derive greater benefit from GIK, particularly in the presence of collateral flow\(^6\).

The mechanism of benefit of GIK infusion is thought to be due to increased glycolysis and reduced FFA uptake and metabolism by myocardial cells\(^7,9\). This has been purported to lead to lower myocardial oxygen requirement, a reduction in proton and free radical accumulation\(^8\), and improved myocardial energetics\(^9\). However, it remains possible that a component of the effects of insulin in reducing susceptibility to ischaemia-induced cellular necrosis may be independent of these metabolic effects\(^10\). Some coronary artery flow is required for GIK to be delivered to the site of myocardial injury during acute MI. Previous studies have demonstrated that during MI, some flow to the infarcted regions persists, due primarily to collateralization.\(^11\) Both the ECLA\(^3\) and Dutch study\(^4\) suggested that GIK was only beneficial when given in concert with reperfusion.

**PERHEXILINE**

Perhexiline was a frequently prescribed antianginal agent in the 1970s. Early randomized controlled trials in patients with coronary artery disease demonstrated that it markedly relieved symptoms of angina, improved exercise tolerance, and increased the workload needed to induce ischemia when used as monotherapy\(^12\). More recently, randomized controlled trials have demonstrated that perhexiline exerts marked, incremental antianginal effects in patients receiving β-blockers\(^13\) or even “triple” prophylactic antianginal therapy\(^14\).

Though originally designated as a calcium-channel blocker, it is clear that it has no significant calcium-channel blocking activity at therapeutic concentrations\(^15\). Perhexiline is not negatively inotropic and does not alter systemic vascular resistance to a significant degree at plasma levels that are within therapeutic range\(^16\). There is now increasing evidence that it acts by shifting myocardial substrate utilization from fatty acids to carbohydrates\(^17\) through inhibition of CPT-1 and, to a lesser extent, CPT-2, resulting in increased glucose and lactate utilization\(^18\).

Perhexiline use declined dramatically in the early 1980s following reports of hepatotoxicity\(^19\) and peripheral neuropathy\(^20\). These effects were later demonstrated to occur most commonly in patients who are “slow hydroxylators”, bearers of a genetic variant of the cytochrome P-450 enzyme family.\(^21\) These patients are slow metabolizers of perhexiline due to saturation of hepatic metabolic pathways, which leads to accumulation of the drug and toxicity. The mechanism for toxicity appears to be due to phospholipid accumulation\(^22\), which is a direct consequence of CPT-1 inhibition. Hence, this is a potential side effect of any drug that inhibits CPT-1, including amiodarone, which exhibits weak CPT-1-inhibitor properties\(^23\). This is thought to be the mechanism responsible for the peripheral neuropathy and hepatitis occasionally seen with amiodarone use.

However, it has since been demonstrated that the risk of toxicity can be dramatically reduced by maintaining plasma concentrations between 150 and 600 ng/mL without compromising the efficacy of the drug\(^24\). Indeed, during short-term therapy the risk of adverse effects is limited to nausea and dizziness associated with elevated plasma levels\(^25\), and hypoglycemia in diabetics. With long-term treatment, there is considerable risk of phospholipidosis-mediated hepatitis or peripheral neuropathy unless the drug is titrated according to plasma levels. Cole et al\(^14\) confirmed the safety of perhexiline in a randomized, double-blind, crossover study following initiation of 100 mg of perhexiline twice daily with subsequent plasma-guided dose titration; none of the patients developed major permanent adverse effects. They also confirmed the sustained clinical efficacy of perhexiline with this strategy by
demonstrating a marked improvement in angina frequency and exercise capacity when perhexiline was added to “triple” prophylactic antianginal therapy.

These findings have led to resurgence in the use of perhexiline in some parts of the world, particularly Australia, for the treatment of refractory angina. However, its use in Europe remains limited. Perhexiline is currently available in most European countries on a named-patient basis, usually as adjunctive treatment for refractory angina in patients not suitable for, or awaiting, coronary intervention, but its use must be accompanied by serum level monitoring.

A recent study has suggested that in patients with chronic stable angina or unstable coronary syndromes, perhexiline may also increase the sensitivity of platelets to the antiaggregatory effects of nitric oxide. It is not yet clear whether this interaction of perhexiline with platelet function reflects changes in platelet CPT activity. This effect may be therapeutically important, especially in patients with unstable coronary syndromes.

In addition, the lack of significant negative inotropic effects of perhexiline, combined with its nonvasoactive properties, has raised its potential utility for angina occurring in the presence of systolic heart failure and/or aortic stenosis. One open-labelled study suggested an improvement in the symptomatic profile of elderly patients with inoperable aortic stenosis. A randomized, double-blind, controlled study investigating this further is presently underway.

Currently, the postulated therapeutic roles for perhexiline are as short-term therapy (less than 3 months duration) in patients with severe ischemia awaiting coronary revascularization or long-term therapy in patients with ischemic symptoms refractory to other therapeutic measures.

TRIMETAZIDINE

Trimetazidine (1-[2,3,4-trimethoxybenzyl] piperazine dihydrochloride – a substituted piperazine compound similar to ranolazine) is a drug that has attracted considerable interest recently. It exhibits no significant negative inotropic or vasodilator properties either at rest or during dynamic exercise. Several clinical trials have demonstrated the potential benefits of trimetazidine in ischemic heart disease. In two separate small studies, trimetazidine was found to increase systolic-thickening scores in ischemic myocardial segments using dobutamine stress echocardiography. A larger, randomized, controlled trial conducted in Poland (TRIMPOL II) recruited 426 patients with stable angina who were randomized to either trimetazidine 20 mg three times a day or placebo in addition to metoprolol. This study demonstrated an improvement in time to ST-segment depression on exercise tolerance testing (ETT), total exercise workload, mean nitrate consumption, and angina frequency in patients randomized to receive trimetazidine. The drug had a favorable side-effect profile. A recent meta-analysis of 12 clinical trials of trimetazidine in stable angina demonstrated a significant reduction in anginal frequency, but only a nonsignificant trend towards prolongation of the duration of treadmill exercise.

However, a large, randomized, placebo-controlled trial recruiting 19,725 patients with acute myocardial infarction in centres across Europe did not demonstrate a short or long-term mortality benefit when intravenous trimetazidine was infused immediately post-MI for 48 h. Subgroup analysis demonstrated a trend towards reduced mortality that was nonsignificant by intention-to-treat but significant when analyzed by protocol group (13.34% vs. 15.10%, p = 0.027). More recently, a small, double-blind, randomized, placebo-controlled study demonstrated improved exercise capacity and ST-segment depression during post-MI exercise testing.

While the potential clinical benefits of trimetazidine are established, the mechanism for its clinical effects is still debated. Kantor et al. demonstrated that trimetazidine reduces the rate of FFA oxidation, with a concomitant 210% increase in glucose oxidation rates during low-flow ischemia. Their data also suggest that the likely route by which this is achieved is through the inhibition of the enzyme long-chain 3-ketoacyl coenzyme A thiolase (LC 3-KAT), which is a crucial enzyme in the β-oxidation pathway.

The clinical efficacy of trimetazidine has been demonstrated in several clinical trials to date and it remains a potential treatment for the future. However, no randomized dose–response trials have been conducted on trimetazidine as of yet, which has led to uncertainty regarding its role, particularly in terms of its safety profile at higher doses. Its effect on the QT interval has not yet been determined at higher doses. A trial is currently underway to address this issue.

RANOLAZINE

Ranolazine ((±)-N-(2,6-dimethyphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)-propyl]-1-piperazineacetamide) is a substituted piperazine compound similar to trimetazidine. On the basis of recently completed phase-3 clinical trials, it appears to offer...
considerable potential. Though the target enzyme by which it exerts its metabolic antianginal action has yet to be determined, ranolazine has been shown to stimulate glucose oxidation and to act as a partial fatty-acid-oxidation inhibitor (pFOX inhibitor)\(^{36}\). The term pFOX inhibitor was coined after it was observed that ranolazine only inhibits fatty-acid oxidation during the periods of elevated plasma FFA levels associated with myocardial ischemia\(^{36}\). As with trimetazidine, MacInnes et al\(^{37}\) could not demonstrate any significant inhibition of LC 3-KAT by ranolazine. However, they did confirm the partial inhibition of \(\beta\)-oxidation by ranolazine in a dose-dependent manner. It seems likely that ranolazine exerts metabolic effects similar to those of trimetazidine and may even act via the same molecular route.

More recently, two studies using far higher doses of ranolazine (up to 1500 mg twice daily) were conducted. The MARISA study (Monotherapy Assessment of Ranolazine in Stable Angina)\(^{38}\) is a randomized, double-blind, crossover study that evaluated 191 patients with chronic stable angina given ranolazine as monotherapy following withdrawal of all other antianginal drugs. During follow-up ETT, patients had a significantly longer time to angina and 1-mm ST-segment depression while on ranolazine than placebo.

The CARISA trial (Combination Assessment of Ranolazine in Stable Angina)\(^{39}\) studied 823 patients with chronic stable angina given ranolazine as monotherapy following withdrawal of all other antianginal drugs. At follow-up ETT, patients had a significantly longer time to onset of ST-segment depression while on ranolazine than placebo.

ETOMOXIR

Etomoxir has yet to be investigated in a randomized controlled trial but ex vivo work suggests that it has potential as an antianginal agent. It was initially introduced as a potential diabetic agent on the basis of its hypoglycemic effects\(^{40}\). It is a potent CPT-1 inhibitor that has been studied extensively in animal models of ischemia, left ventricular hypertrophy, and left ventricular impairment. In palmitate-perfused ischemic rat hearts, etomoxir reduced oxygen consumption during ischemic recovery and also prevented depression of myocardial function\(^{41}\). Turcani and Rupp\(^{42}\) perfused pressure-overloaded, hypertrophic, and failing rat hearts with etomoxir, leading to an improvement in indices of left ventricular dysfunction.

To date, only one clinical trial has looked at the potential benefits of etomoxir in the human heart. In this open-label, uncontrolled, pilot study conducted in 15 patients with New York Heart Association Class II-III heart failure, etomoxir 80 mg was administered daily\(^{43}\). Following 3 months of open-label treatment, patients had improved left ventricular ejection fraction, cardiac output at peak exercise, and clinical status. However, there are currently no studies examining the long-term safety of etomoxir. As with all CPT-1 inhibitors, it has the potential to cause phospholipidosis. The potency of etomoxir has yet to be established.

DICHLOROACETATE

Dichloroacetate is a specific inhibitor of pyruvate dehydrogenase kinase. As a result, this compound stimulates pyruvate dehydrogenase activity and increases oxidation of pyruvate. This enhances carbohydrate oxidation in preference to fatty acids. In addition, the presence of dichloroacetate results in increased utilization of lactic acid, so that the lactic acid levels that rise during periods of ischemia are preferentially metabolized. There are limited clinical trials with Dichloroacetate.

L-CARNITINE

During ischemia, there are substantial increases in intracellular levels of lysolecithins, free arachidonic acid and acylcarnitines as well as substantial decreases in free carnitine levels. There are also depressed activities of acylcarnitine transport enzymes during ischemia. L-carnitine is the biologically active isomer of carnitine.
and supplementation of this molecule is believed to protect cardiac cells against oxidative stress, hypoxia and ischemia. Carnitine may be cardio protective by its effect of decreasing levels of toxic coenzyme A derivatives or it is beneficial due to up regulation of carbohydrate metabolism. A randomized multicentric trial showed fewer deaths and lesser clinical heart failures in carnitine group.

CONCLUSION

“Metabolic” antianginal therapies induce a shift from free fatty acid towards predominantly glucose utilization by the myocardium to increase ATP generation per unit oxygen consumption. Three such agents (trimetazidine, ranolazone, and perhexiline) have well-documented anti-ischemic effects. However, perhexiline, the most potent agent currently available, requires plasma-level monitoring to avert hepatoneurotoxicity. Trimetazidine and ranolazone do not cause phospholipidosis due to their relatively weak CPT-1 inhibitor properties and seem to act further downstream in the FFA metabolic pathway. Plasma-level monitoring for these two agents is therefore not generally required. However, the long-term safety of both agents, in particular ranolazone, has yet to be established.

Aside from their more established roles as antianginal drugs in coronary artery disease, these agents, in theory, would also be beneficial to patients with angina secondary to hypertrophic cardiomyopathy and aortic stenosis due to their anti-ischemic effects in the absence of vasodilatation. In addition, the potential for their use in chronic heart failure is gaining recognition as data emerge showing the improvement of myocardial function following treatment with several of these drugs.

Future applications for this line of treatment show a great deal of promise and warrant additional research. In particular, large, randomized, controlled trials investigating the effects of these agents on mortality and hospitalization rates due to coronary artery disease are required.

REFERENCES