

## CHAPTER

# 54

## *Early Metabolic Intervention in the Management of Coronary Artery Disease*

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### **Introduction**

The prevalence of ischemic coronary artery disease (CAD) continues to be on the increase globally, more so in India. Indian spectrum of disease seem to be different in terms of early onset as well as complexity in presentation. Therapeutic options include pharmacological therapy, percutaneous coronary interventions (PCI), Coronary artery bypass surgery (CABG), and newer modalities of treatment like external enhanced counter pulsation (EECP) and spinal cord stimulation.

Pharmacological approach to CAD deals mainly by altering the hemodynamics of supply Vs demand mismatch. Nitrates, beta blockers and calcium blockers are the main agents in this mechanism and are known to be effective. However we have a significant number of patients who continue to have significant angina or congestive heart failure in spite of using various available conventional therapies. Resistant angina is a practical problem where in patients continue to have angina in spite of treatments with available hemodynamic agents. It's been estimated that well over 50% of patients experience angina following PCI, and more than 70% report occurrence of angina 1- to 15 years following CABG.<sup>1,2</sup> This brings in the need for newer modalities and approach to the treatment, where in metabolic management, seem to be an important factor.

### **Metabolic management**

Metabolic management is a concept where in drugs are used to improve the outcome in ischemic heart disease by altering the ischemic cell metabolism favorably. Infact various abnormalities of metabolism are reported with ischemic heart disease and failing heart, that would result in malfunctioning of the cell, with resultant altered hemodynamic performance of the heart. Metabolic agents reset this internal metabolic environment favorably resulting in better performance outcomes.

Under aerobic conditions the predominant energy substrate used by myocardial cell to produce ATP are the Free Fatty Acids (FFA). Infact two third of the ATP energy production occurs through this route only. FFAs enter the cell cytoplasm and undergo beta oxidation in mitochondria that yields Acetyl CoA. This Acetyl CoA enters the Krebs cycle to yield ATPs which contribute energy for contraction and relaxation. Glucose by way of glycolytic pathway becomes pyruvate contribute to approximately one third of energy production. Acetyl CoA is produced from pyruvate by the action of pyruvate dehydrogenase, which then enters Krebs cycle to yield ATPs.

On comparison FFAs yield more ATP energy at the expense of more oxygen only under aerobic conditions. During myocardial ischemia with lack

of oxygen the metabolism is more dependent on glucose metabolism. As the FFAs continue to be available as an energy substrate, it inhibits pyruvate dehydrogenase which in turn allows accumulation of pyruvate which would become lactate resulting in intra cellular acidosis. This impairs the cellular function of contraction and relaxation.<sup>3</sup>

Therapeutic suppression of FFA uptake or switching over to oxygen source of energy ATP production during ischemia therefore may be an alternative option in the treatment of CAD. To summarise it may be said that metabolic agents aim a different target, inside the cell producing cost effective ATP as a source of energy during myocardial cell ischemia.

The other rationale for using metabolic agents early in the treatment of angina may be due to the fact that as many as 5 to 15% of the patients with stable angina may be refractory to triple therapy using hemodynamic agents and yet not considered for revascularization.<sup>4,5</sup>

European society guidelines (ESC 2006 guidelines) now recommend these agents as a class II b option in the treatment of stable angina pectoris as an add on therapy or as substitution therapy when conventional drugs are not tolerated (Level of evidence B).<sup>6</sup>

Under metabolic agents we shall discuss Ranolazine, Trimetazidine and Ivabridine in detail.

### **Ranolazine**

Ranolazine is a novel antianginal agent. It is an orally active piperazine derivative with a selective inhibition of the late sodium current. This action reduces the magnitude of ischemia induced sodium and calcium overload and thereby improves myocardial function as well as myocardial perfusion.<sup>7</sup>

<sup>8</sup> The agent is a known inhibitor of myocardial fatty acid oxidation, resulting in preferential glucose oxidation.<sup>10</sup> The glucose pathway requires less oxygen for a given level of myocardial work, and this increased "oxygen efficiency" may be an important component of the antiischemic action. The drug has been recently approved by US FDA

for treatment in angina and is now available in India.

The anti anginal effects of ranolazine are not dependent on reduction of heart rate or blood pressure or on increase in coronary blood flow. During exercise testing, patients are able to achieve an increased rate pressure product at maximal exercise compared with placebo or beta- blocker.<sup>9</sup>

Ranolazine is well tolerated; the principal side effects include dizziness, nausea, asthenia, constipation, and headache. Of concern is its propensity to dose-related prolongation of the QTc, the net effect of its inhibition of IKr, late INa, and late ICa. However, there has been no evidence of increased dispersion of repolarization or any documented cases of torsades de pointes. Ranolazine is metabolized in the liver and excreted in the urine and so is contra-indicated in hepatic impairment. It is metabolized primarily by CYP3A, (hepatic cytochrome) which is potently inhibited by diltiazem and verapamil, neither of which should be used concurrently. Ranolazine inhibits metabolic pathways for simvastatin and digoxin, and dose reductions of these agents may also be required.<sup>10</sup>

The monotherapy Assessment of Ranolazine in Stable Angina (MARISA) trial investigated the antiischemic effects of ranolazine and long term survival of 191 patients with chronic severe angina. Treatment with ranolazine resulted in a 24 to 56 second improvement in exercise tolerance in patients who took 500 to 1500 mg of ranolazine twice daily.<sup>11</sup>

The combination Assessment of Ranolazine in Stable Angina (CARISA) trial investigated the effect of ranolazine in combination with other antianginal agents. In this phase 3 double blind, placebo-controlled clinical trial, 23 patients with refractory angina, receiving standard therapy with atenolol, diltiazem or amlodipine, were randomized to placebo, ranolazine at 750 mg twice daily or ranolazine at 1000 mg twice daily. After 12 weeks, patients in both ranolazine arms had 26% increase

in total exercise time and a decrease in the number of anginal episodes per week, although the time to onset of 1 mm ST-segment depression during exercise testing did not change.<sup>12</sup>

The ERICA (Efficacy of Ranolazine In Chronic Angina) trial demonstrated that ranolazine was an effective antianginal agent in patients with stable CAD and refractory angina despite a maximum recommended dosage of amlodipine. Addition of 1000 mg ranolazine twice a day significantly reduced the frequency of angina episodes and rate of nitroglycerine consumption. Ranolazine was well tolerated; most adverse effects were mild to moderate, and antianginal efficacy was unrelated to changes in blood pressure or heart rate.<sup>13</sup> Ranolazine is a promising antiischemic drug that may be valuable in a wide variety of subsets of patients with CAD who remain symptomatic despite treatment with other hemodynamic agents.

Because ranolazine prolongs the QTc interval, the FDA approval is limited to patients who have not responded to other antianginal drugs, and its use in combination with amlodipine, beta-blockers, or long-acting nitrates. The daily dose should be limited to 1000 mg and precautions are advised regarding QTc prolongation.

### **Trimetazidine**

Trimetazidine is a unique fatty acid oxidation inhibitor and acts via selective inhibition of 3-ketoacyl CoA thiolase [3KAT]. During ischemia the drug allows to utilize glucose as an energy source by blocking fatty energy source. This results in energy efficient ischemic cell. Its efficacy in the treatment of angina has been evaluated in a number of studies as monotherapy, in combination, in acute and chronic administration, as an initial treatment or in patients resistant to beta blockers or calcium channel blockers.<sup>14, 15</sup> Trimetazidine, European Multicenter Study (TEMS) included patients with stable angina and documented CAD, who were randomly assigned to treatment with trimetazidine or propranolol orally for 3 months. The time to ST-segment depression on exercise testing and the time

to onset of symptomatic angina were comparable in both groups.<sup>16</sup> In another study, trimetazidine was added to standard antianginal therapy with long-acting nitrates, calcium channel blockers, and beta blockers. After four weeks, there were significant reductions in the number of symptomatic episodes of angina and improvements in the time to ischemia related ECG changes on exercise testing.<sup>17</sup>

In a large recently published meta analysis, twelve clinical studies of trimetazidine performed between 1985 and 2001 were evaluated. Trimetazidine emerged as an efficacious agent in the treatment of angina pectoris both as monotherapy and in combination with other antianginal agents. Trimetazidine significantly reduced the number of symptomatic anginal episodes and improved the time to objective, exercise induced ECG changes.<sup>18</sup>

The mechanism of action of trimetazidine, a 3KAT inhibitor based on a switch from fatty acids to glucose utilization makes this drug an attractive treatment for angina pectoris in diabetic patients also. The TRIMPOL – I trial had shown that, four weeks of treatment with trimetazidine resulted in a significant improvement in exercise capacity and exercise duration in the subgroup of diabetic patients.<sup>19</sup> TRIMPOL-II study has shown that trimetazidine provides anti-anginal efficacy in post revascularized patients with recurrent angina despite a monotherapy with metoprolol.<sup>20</sup> This agent is available in India with widespread usage.

Trimetazidine has got beneficial effect on patients with left ventricular dysfunction, also as reported in an elegant trial conducted by Lu et al.<sup>21</sup>

### **Ivabridine**

Ivabridine, a selective sinus node 'If' or 'funny' current channel inhibitor, represents a therapeutic innovation in the treatment of CAD. Preclinical and early clinical studies show that ivabridine can reduce the heart rate without affecting cardiac systolic function, suggesting that 'If' inhibition may be an effective approach to minimise angina and the underlying ischemia. Furthermore, the

absence of adverse cardiac effects associated with If inhibition suggest that this approach may be effective in other patient groups, such as those at risk of acute coronary events or compromised left ventricular function.

The INITIATIVE trial (INternatIonal TrIAL on the treatment of angina with IVabridinE versus atenolol) assessed the antianginal and anti ischemic effects of ivabridine compared with the beta blocker, atenolol. Selective If inhibition with ivabridine treatment produced similar antianginal and antiischemic effects to atenolol both after one month and four months of treatment. At four months, total exercise duration increased by 86.8 seconds with atenolol (100 mg). Ivabridine was at least as effective as atenolol in time to limiting angina and time to 1mm ST segment depression. The most frequent adverse drug reaction associated with ivabridine is visual symptoms, consisting mainly of increases in brightness in limited areas of the visual field, which are transient and do not disturb patient activities.<sup>22</sup> Further clinical trials with Ivabridine to evaluate fully the therapeutic potential of If inhibition are ongoing.

## Conclusion

Coronary artery disease a major health burden continues to pose us problems in management either by presentation or while on treatment. Refractory angina is a real problem which may need a combination of hemodynamic agents with a metabolic agent. By altering the metabolism favorably, these agents have a promising future of its own in the armamentarium of agents for treatment of CAD. Ranolazine, Trimetazidine and Ivabridine have some evidence as metabolic agents in the treatment of CAD, and its very clear now that these agents have an important role to play in the management of CAD. Future would let us know about their role either they are more of adjunctive therapy or as an early therapy in CAD.

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