INTRODUCTION

Coronary Artery Disease (CAD) is one of the major causes of morbidity and mortality the world over. Although treatment of stable CAD has all along been based on conventional medical therapy including beta blockers, antiplatelets, nitrates, Calcium blockers, ACEI and statins, recently the role of metabolic management of CAD is being increasingly recognized.

ROLE OF METABOLIC THERAPY IN CAD

Myocardial ischemia is the metabolic consequence of reduced blood supply to the myocardium. Under normal conditions the heart derives most of its energy from Free Fatty Acid (FFA) oxidation with the rest from glucose oxidation and lactate. When there is hypoxia due to reduced myocardial perfusion the myocardial cells respond by accelerating glucose uptake to generate sufficient ATP to maintain ionic gradients and calcium homeostasis. This is because glycolysis requires less oxygen per mole of ATP generated compared to FFA oxidation. When there is severe ischemia, there is an imbalance between the oxygen requirement of myocardial cells and coronary blood supply. This results in metabolic, morphological and functional alteration of the myocardium leading to arrhythmias, contractile failure and electrophysiological abnormalities. At the cellular level glucose uptake is decreased and conversion to lactate is increased, resulting in cell acidosis. The FFA pathway slows down leading to less ATP production. These metabolic alterations ultimately lead to cell death. Hence it seemed logical that if drugs were developed to manipulate the myocardial energy metabolism by promoting glucose oxidation, they may protect the myocardial cells from ischemic injury.

Stimulation of myocardial glucose oxidation can be achieved directly by stimulating glucose oxidation (or) indirectly by inhibiting FFA oxidation thereby shifting energy substrate utilization towards glucose metabolism.

A number of pharmacological agents that cause metabolic modulation are available and these can be broadly classified as
1. Drugs that inhibit FFA oxidation
   a. 3-Ketoacyl coenzyme A Thiolase (3-KAT) inhibitors → Trimetazidine
   b. Carnitine Palmitoyl Transferase (CPT)-1 inhibitors - Etomoxir, Perhexiline, Oxfenicine
2. Drugs that probably inhibit FFA oxidation
   a. Late Inward sodium channel blockers → Ranolazine
3. Drugs that stimulate glucose oxidation
   a. L-Carnitine
   b. Mitochondrial metabolic oxidants - Coenzyme Q, Lipoic Acid
   c. Dichloroacetate
   d. Ribose

3-KAT INHIBITORS - TRIMETAZIDINE

This class of drugs act by increasing glucose and lactate oxidation secondary to a partial inhibition of fatty acid oxidation. Trimetazidine is the most widely used and also widely studied in this class of drugs. This drug acts by inhibiting the mitochondrial long chain 3 Ketoacyl coenzyme A Thiolase, the last enzyme involved in FFA Beta oxidation. Reduction of FFA oxidation results in increase of glucose oxidation leading to ATP production with less oxygen consumption. Trimetazidine also
Ranolazine has been shown to significantly reduce anginal concentration, voltage and frequency dependent manner. Ranolazine plays an important role in late INa channels in a major metabolic and electrophysiological disturbances. This intracellular sodium overload causes oxidative stress. This intracellular sodium overload causes major metabolic and electrophysiological disturbances. Ranolazine plays an important role in late INa channels in a concentration, voltage and frequency dependent manner. The effect is more pronounced in ischemic myocytes. Ranolazine has been shown to significantly reduce anginal episodes and nitroglycerine use and significantly improve exercise duration and time to exercise induced myocardial ischemia in patients with stable CAD. Various trials including the Monotherapy Assessment of Ranolazine in Stable angina (MARISA), the Combination Assessment of Ranolazine in Stable Angina (CARISA) and Efficacy of Ranolazine in Chronic Angina (ERICA) have shown a significant benefit with Ranolazine in stable angina patients. It has not been proven to have a clear cut mortality benefit. Like Trimetazidine the European Society of Cardiology has recommended its use only as an adjunctive therapy in patients with angina.

**L-CARNITINE**

It is a co factor of Fatty acid metabolism. It enhances the FFA metabolism. It also increases glucose oxidation. Many human and animal studies have shown only a modest benefit in terms of left ventricular energetics and function with L-carnitine use. Recent animal studies have shown L-carnitine to have an antiarrhythmic effect in ischemic heart disease, giving credence to the previous preliminary observations on the antiarrhythmic effect of L-carnitine in humans with CAD. The lack of significant clinical studies have resulted in L-Carnitine not being recommended for routine use in patients with CAD.

**MITOCHONDRIAL METABOLIC OXIDANTS: → COENZYME Q & LIPOIC ACID**

Coenzyme Q (Ubiquinone) is a mitochondrial coenzyme which is essential for the production of ATP. Lipoid acid is a cofactor for pyruvate dehydrogenase enzyme system. The presence of these molecules helps the mitochondria defend itself against the harmful effects of the oxygen atmosphere. Lipoic acid enhances glucose metabolism. Coenzyme Q is an excellent antioxidant. Co Q decreases blood viscosity and improves blood flow to cardiac muscle in patients with CAD. CoQ recently has been shown to improve endothelial function by inhibiting nitric oxide oxidation. It has also been shown to be beneficial in heart failure patients. However further studies are warranted before CoQ therapy is recommended for both CAD and Heart failure.

**DICHLOROACETATE**

Dichloroacetate acts by promoting glucose metabolism and to some extent by inhibiting fatty acid oxidation promoting glucose metabolism during periods of myocardial ischemia. It activates Pyruvate dehydrogenase complex, the rate limiting step of glucose oxidation. Experimental studies on humans and animals have shown dichloroacetate to improve the LV systolic volume, decrease systemic vascular resistance, stimulate myocardial lactate consumption and improve left ventricular mechanical efficiency with a simultaneous reduction in myocardial oxygen consumption. However its short half life and lack of significant clinical studies have not allowed its clinical use in cardiac patients.
RIBOSE
Ribose is a pentose sugar. It has been shown to enhance ATP production and improve cardiac function in many animal experiments. Ribose enhances glucose metabolism. In small studies ribose has shown significant improvement in time to ST segment depression and time to moderate angina during treadmill testing when compared to placebo. Ribose has also been shown to improve diastolic function. As it has no adverse reactions and does not have any hemodynamic effects it is an alternate option in treatment of CAD. However because of lack of significant studies and consensus its role in the therapy for CAD is yet to be defined.

CONCLUSION
These group of drugs which cause metabolic modulation of the myocardial cells present a novel approach in management of CAD as well as Heart failure. However as significant randomized double blinded studies have not been done with these agents to show a reduction in mortality they will not be recommended as primary therapy in CAD and Heart failure. With the available evidence these agents can be used as adjunctive therapy to the tried and tested hemodynamic agents in management of CAD. However the discovery of these agents have held great promise and has opened up new therapeutic options paving many ways to

REFERENCES