Cardiac metabolism treatment for myocardial ischemia
Dr. Giuseppe Rosano

Despite treatment with haemodynamic drugs angina remains a significant health problem for many patients with ischemic heart disease. It has long been shown that haemodynamic anti-ischemic drugs do not have a significant additive effect while the combination of haemodynamic agents with drugs that improve cardiac metabolism is an effective treatment for myocardial ischemia.

Hemodynamic combined therapy

Study	Combinations	Findings
Akras *et al* . *Lancet* 1991;338:1036–1039	Atenolol Atenolol + nifedipine SR Atenolol + ISMN Atenolol + ISMN + Nifedipine SR	No substantial benefit to any combination over betablocker monotherapy
Meyer TE *et al* . *Cardiovasc Drugs Ther* 1993;7:909–913	Atenolol Nifedipine SR Atenolol + nifedipine SR	Combination therapy is no better than atenolol alone
Madjlessi-Simon T *Eur Heart J* 1995;16:1780–1788	Beta- blocker Beta- blocker + amlodipine	Combination provides no additional benefit in patients resistant to beta-blocker

Hemodynamic combined therapy

TIBET. Fox K Eur Heart J 1996;17:96–103	Atenolol Nifedipine SR Atenolol + nifedipine SR Atenolol + nifedipine SR 608 patients included	No additive benefit from combined therapy.
IMAGE. Savonitto J Am Coll Cardiol 1996;27:311–316	Metoprolol Nifedipine SR Combined therapy 249 inclusions	No additional benefit when Calcium Channel blocker is adjuncted to A beta-blocker
CESAR. Knight C and Fox KM Am J Cardiol 1998;81:133–136	Amlodipine + Atenolol vs Diltiazem + Atenolol	Exercise test parameters do not improve when adding a second hemodynamic drug

Under non-ischemic conditions the majority of of ATP formation in the healthy heart comes from oxidative phosphorylation in the mitochondria, with the remainder derived from glycolysis and GTP formation in the citric acid cycle. The heart has a relatively low ATP content and has a complete turnover of the ATP pool approximately every 10 seconds. Approximately 60–70% of ATP is used for contractility, and the remaining 30–40% is primarily used for the sarcoplasmic reticulum Ca^{2+}-ATPase and other ion pumps.

The regulation of myocardial metabolism is linked to substrate availability, coronary flow, inotropic state, and hormonal regulation. The citric acid cycle is fuelled by acetyl-CoA formed from decarboxylation of pyruvate and from β-oxidation of fatty acids. In the healthy heart the rates of flux through the metabolic pathways linked to ATP generation are set by the requirement for external power generated by the myocardium and the rate of ATP hydrolysis.

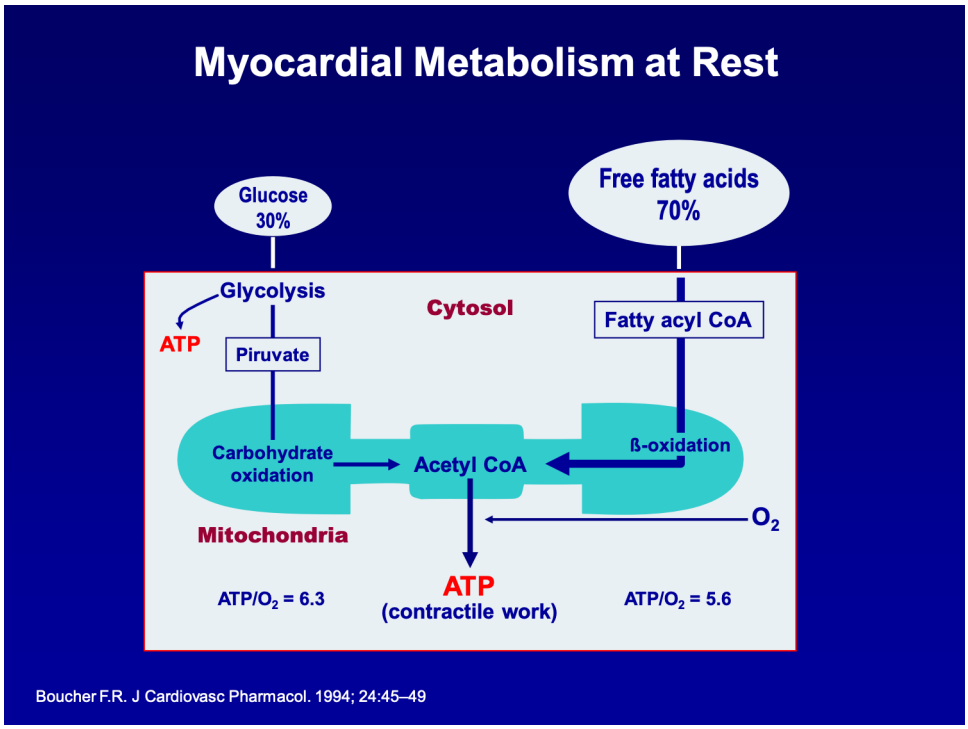
In the normal heart, ~60–80% of the acetyl-CoA comes from β-oxidation of fatty acids, and 20–40% comes from the oxidation of pyruvate produced in nearly equal amounts from glycolysis and lactate oxidation. The glycolytic pathway converts glucose 6-phosphate and NAD^+ to pyruvate and NADH and generates two ATP for each molecule of glucose. The NADH and pyruvate formed in glycolysis are either shuttled into the mitochondrial matrix to generate CO_2 and NAD^+ and complete the process of aerobic oxidative glycolysis or converted to lactate and NAD^+ in the cytosol. The healthy nonischemic heart is a net consumer of lactate even under conditions of near-maximal cardiac power. The myocardium becomes a net lactate producer only when there is accelerated glycolysis in the face of impaired oxidation of pyruvate, such as occurs with ischemia or diabetes mellitus. The oxidation of glucose and pyruvate and the activity of PDH in the heart are decreased by elevated rates of fatty acid oxidation, such as occur if plasma levels of free fatty acids (FFA) are elevated or if the glucose uptake is impaired.

The rate of fatty acid uptake by the heart is primarily determined by the concentration of nonesterified fatty acids in the plasma. Under conditions of metabolic stress, such as ischemia, diabetes, or starvation, plasma FFA concentrations can increase to much higher levels (>1.0 mM). Free fatty acids are highly hydrophobic and are never truly free in vivo but rather are associated with proteins or covalently bound to coenzyme A or carnitine. Fatty acid β-oxidation occurs primarily in the mitochondria and to a small extent in peroxisomes. The primary products of fatty acid oxidation are NADH, $FADH_2$, and acetyl-CoA. Once taken up by the mitochondria, fatty acids undergo β-oxidation. This process involves four reactions. The final step is modulated by 3-ketoacyl-CoA thiolase (3-KAT), which regenerates acyl-CoA for another round of β-oxidation and releases acetyl-CoA for the citric acid cycle.

The primary physiological regulator of the rate of glucose oxidation in the heart is the rate of fatty acid oxidation. High rates of fatty acid oxidation inhibit PDH activity via an increase in mitochondrial acetyl-CoA/free CoA and NADH/ NAD^+, which activates PDH kinase causing phosphorylation and inhibition of PDH.

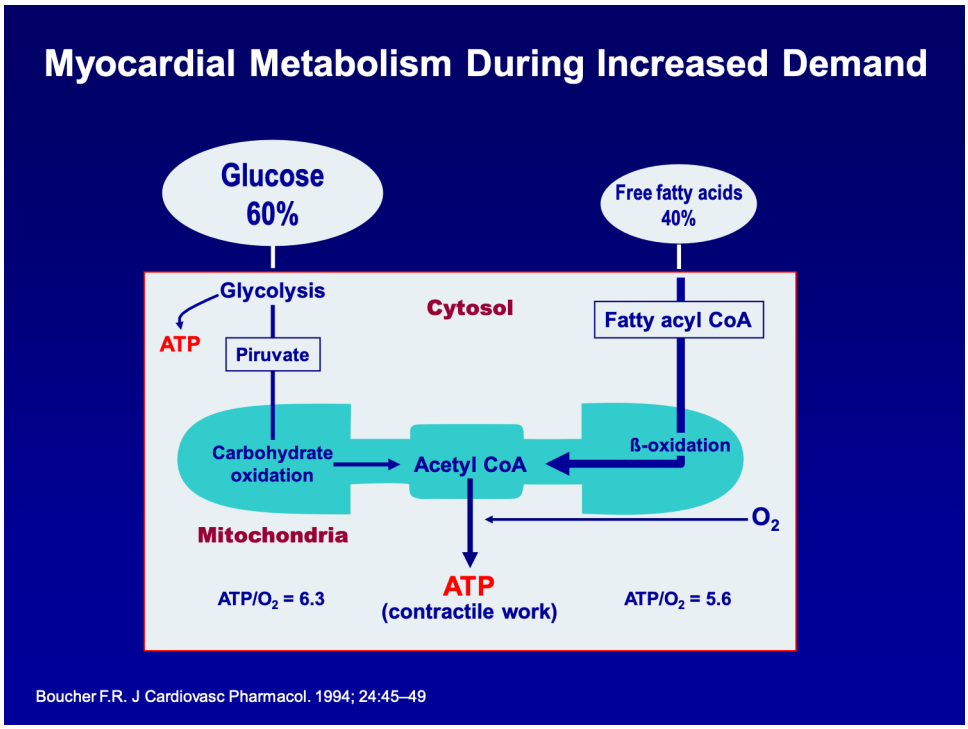
Conversely, inhibition of fatty acid oxidation increases glucose and lactate uptake and oxidation by decreasing citrate levels and inhibition of PFK and lowering acetyl-CoA and/or NADH levels in the mitochondrial matrix, thereby relieving the inhibition of PDH.

Therefore, the healthy adult human heart at rest is able to adopt substrate utilisation accordingly to circumstances but in general approximately 70% of energy production is derived from beta oxidation of fatty acids.

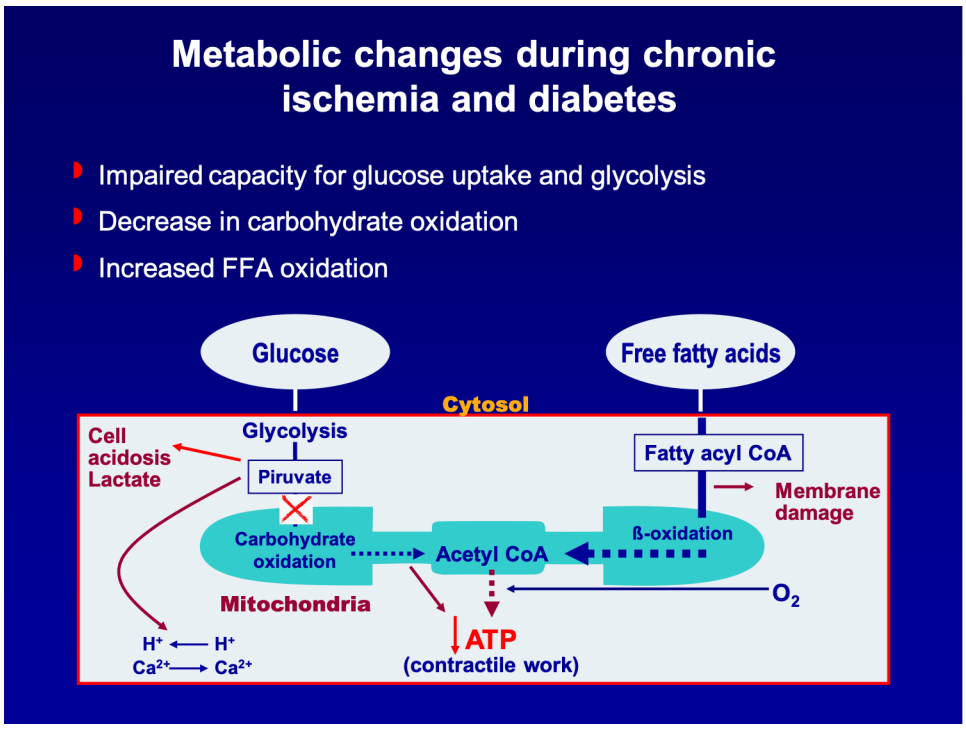


During increased metabolic demands, like in case of increased heart rate or blood pressure, in the normal human heart there is a shift towards greater glucose utilisation suggesting that the heart utilizes at rest the least effective source of energy production (FFA) in order to store glucose for periods of increased metabolic demands. Indeed, carbohydrate oxidation is more effective than

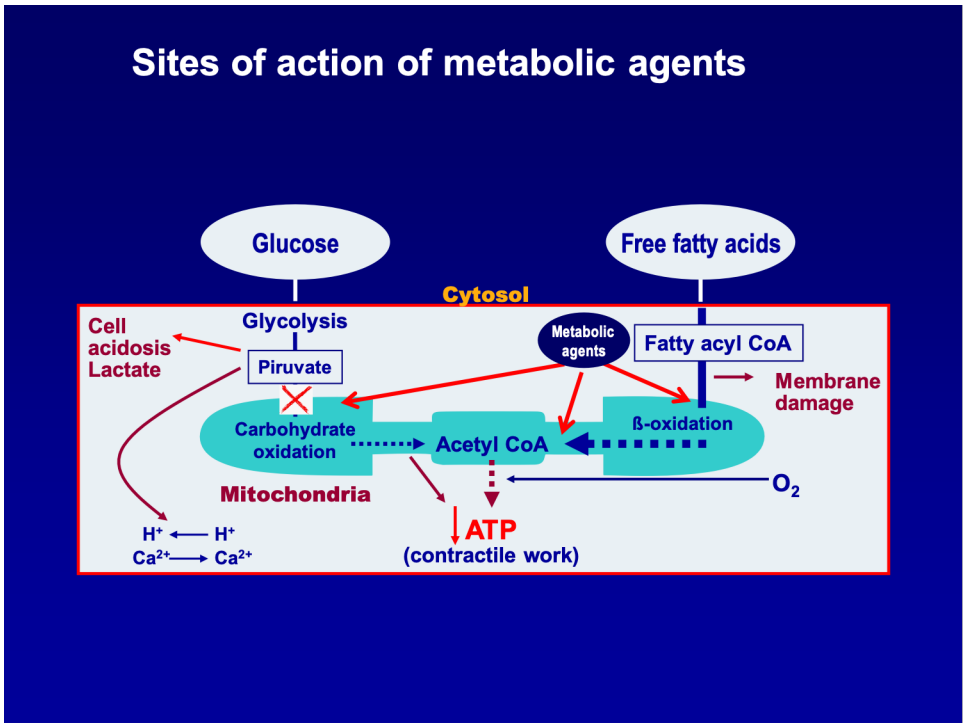
FFAs oxidation in producing ATP.



The changes that occur during increased metabolic demands also occur during ischemia or in patients with diabetes mellitus where there is a shift towards greater glucose utilisation, but free fatty acid utilisation is still around 50%.



The "Metabolic" antianginal drugs optimizing fatty acid metabolism induce a shift from free fatty acid towards glucose utilisation thereby increasing energy production for a given amount of oxygen.



Classification of myocardial metabolic agents

- **FFA uptake inhibitors**

Perhexiline

Oxfenicine

Etmoxir

- **FFA β-Oxidation inhibitors**

Trimetazidine

- **Others**

D-Ribose

Proprionyl-L-Carnitine

Glucagon-like Peptide-1

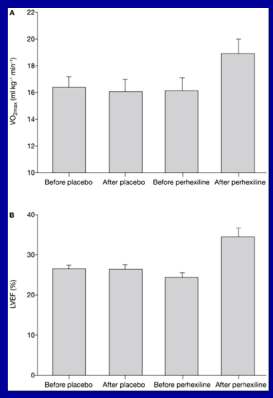
Only few substances proven effective in modulating cardiac metabolism are commercially available. Of these the only two drugs that have been shown to improve myocardial ischemia are parexhelline and trimetazidine

Modulators of Cardiac Metabolism

	Metabolic effect at farmacological doses	Anti-ischemic effect	Major SE	Marketed
Trimetazidine	FFA inhibitor	++++	GI	Worldwide
Perhexiline	CPI inhibitor	+++	Liver toxicity	Australia
Etomoxir	CPI inhibitor	----	LVH, Lynphoma	No
Niacin	Uptake inhibitor	----		Worldwide
Ranolazine	None	+---	QT, Liver	US
Dichloroacetate	Inhib PDH kinase	+++		No

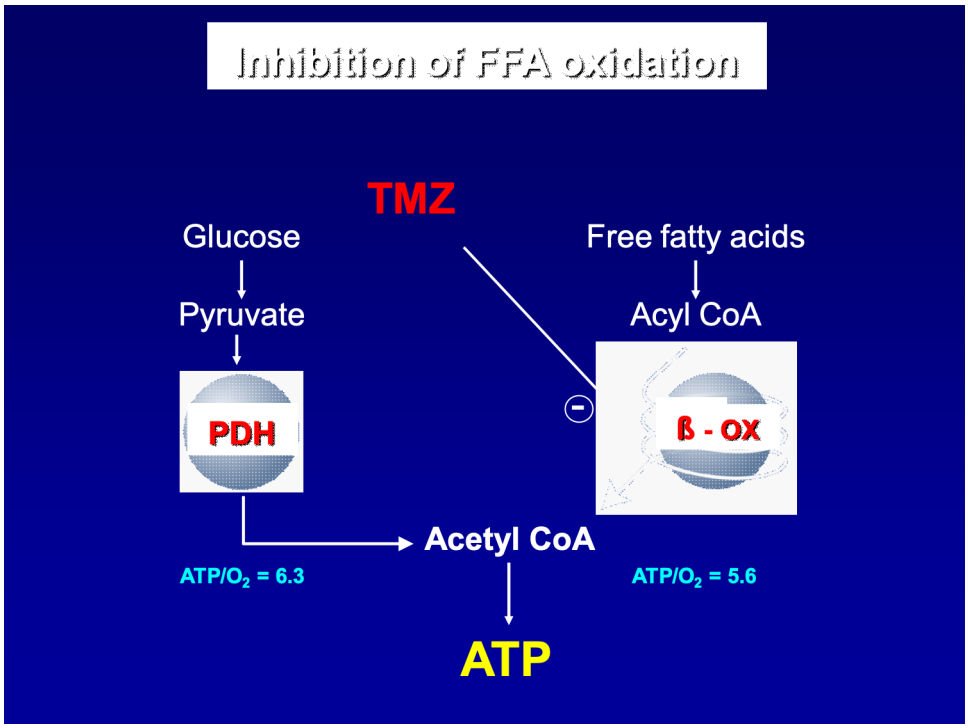
Trimetazidine and Perhexiline are the only two metabolic agents with proven anti-ischemic effect

Effect of perhexiline treatment in patients with ischemic or nonischemic heart failure

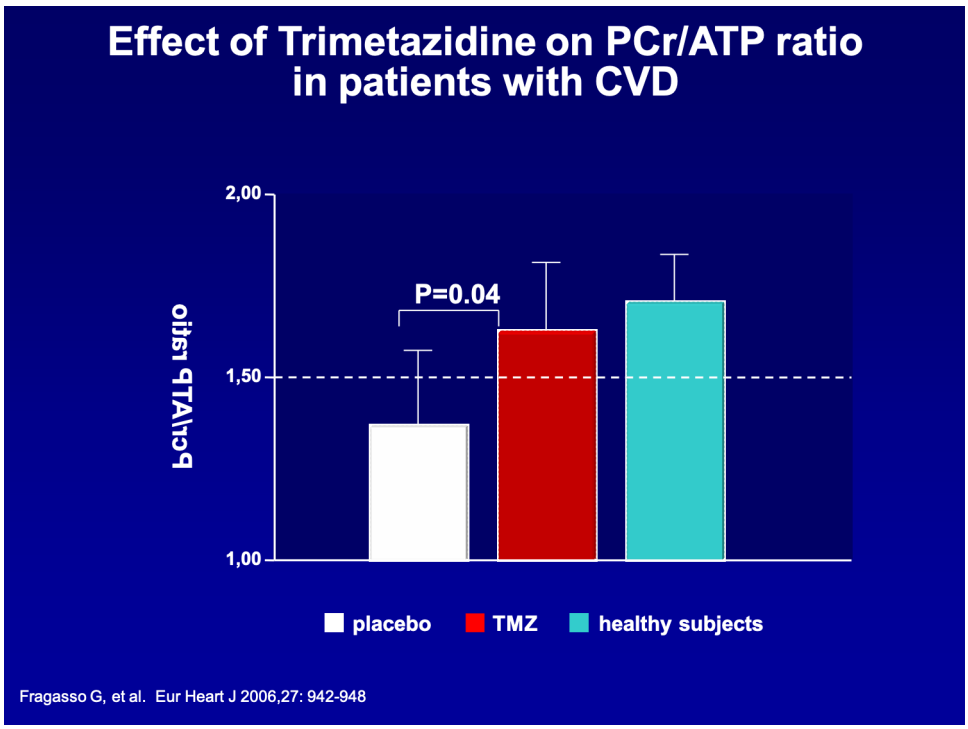


Reproduced from Lee L *et al*. (2005) Metabolic modulation with perhexiline in chronic heart failure: a randomized controlled trial of short-term use of a novel treatment. *Circulation* **112**: 3280–3288. © (2005 Lippincott, Williams & Wilkins.

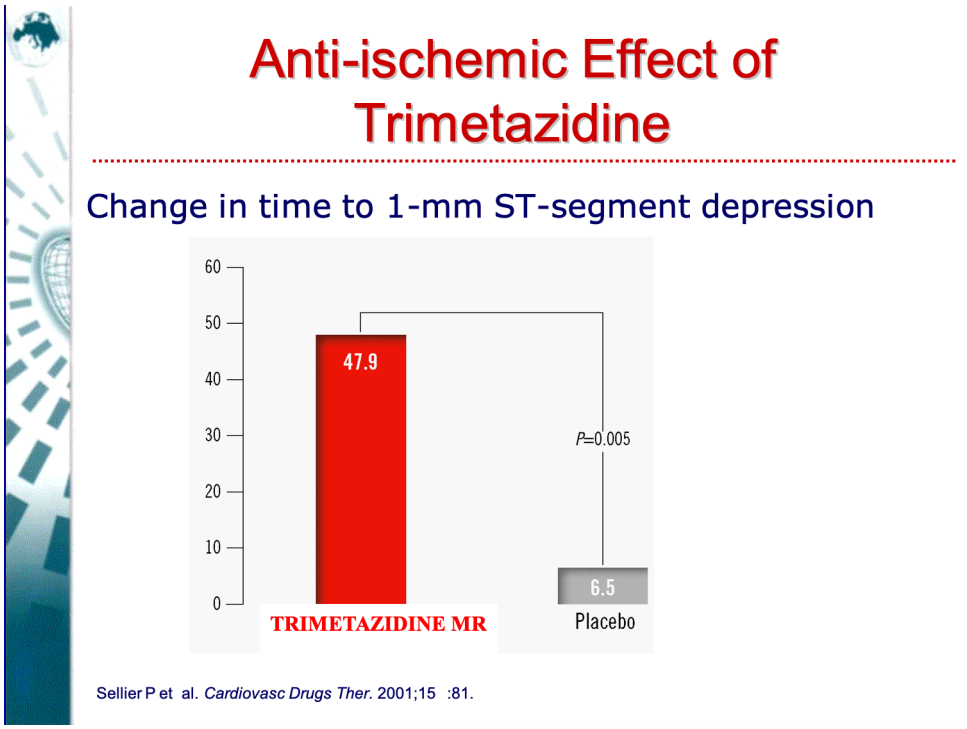
Trimetazidine has been shown to modulate cardiac metabolism through an inhibition of beta-oxidation at the 3-KAT enzyme. The inhibition of FFA oxidation leads to a greater use of glucose and glycogen as energy substrate with a greater mechanical efficiency during ischemia.



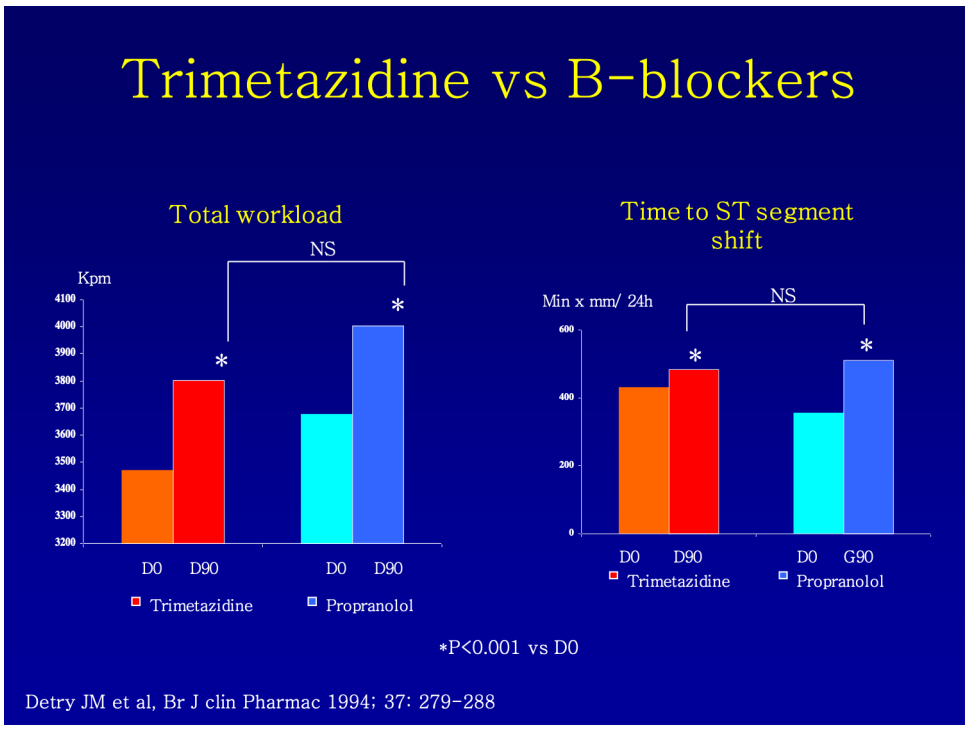
The metabolic effect of trimetazidine on myocardial energy production has been recently proven in vivo by Fragasso et al who showed that in patients with coronary artery disease trimetazidine normalizes the PCr/ATP (Phosphocreatine/ATP).



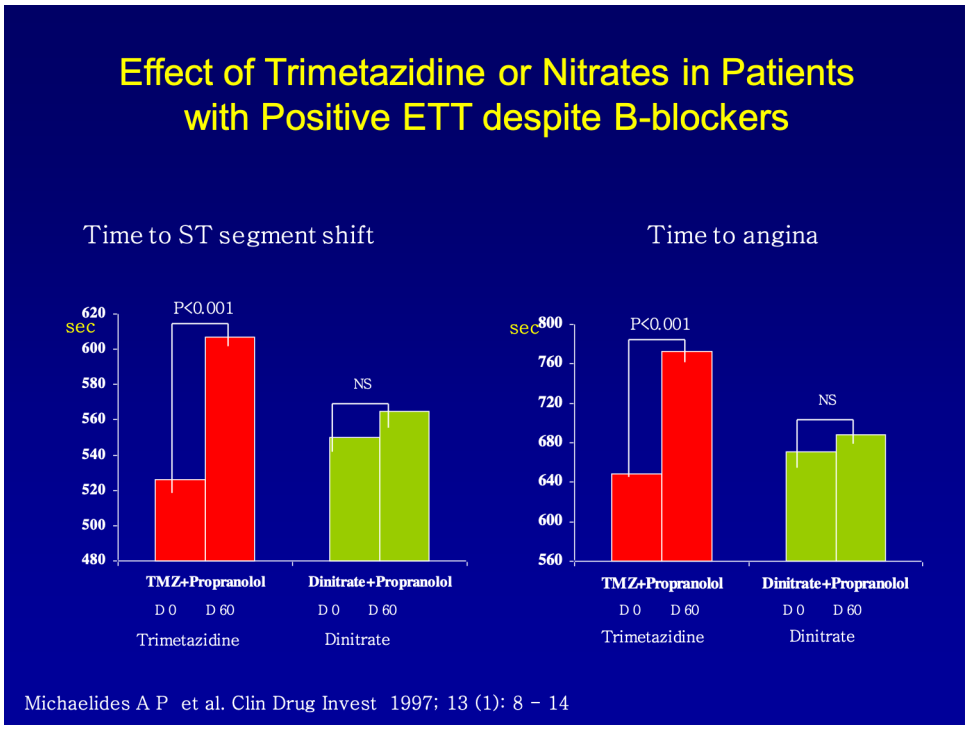
Trimetazidine is an effective anti-ischemic agents and several studies have shown that trimetazidine significantly prolongs both time to 1 mm ST depression and exercise time in patients with myocardial ischemia.



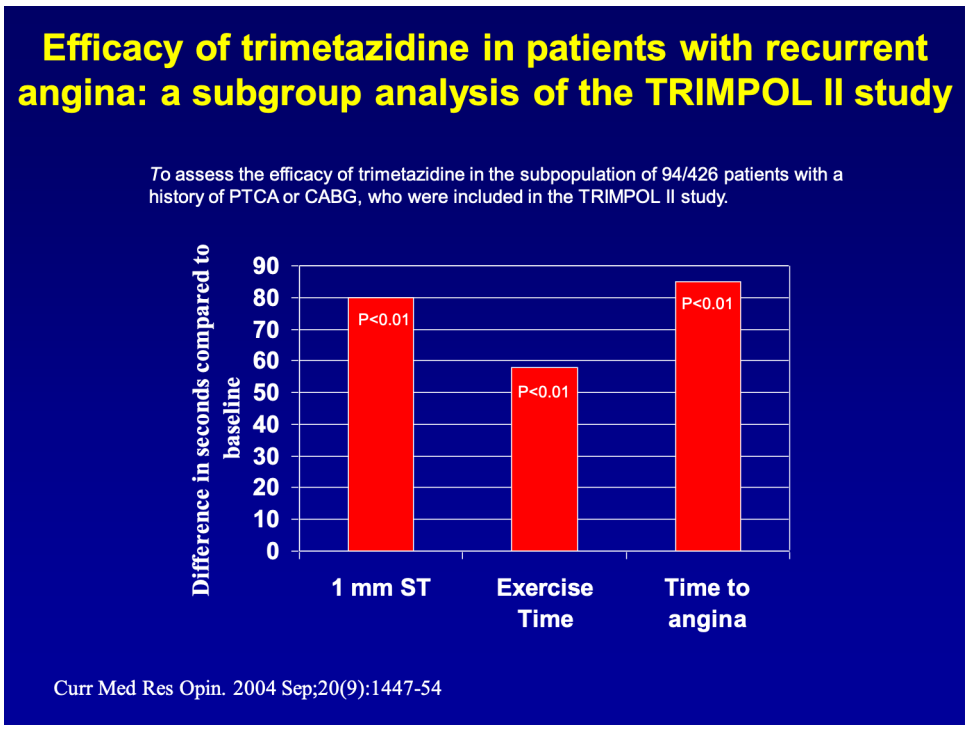
Trimetazidine has been shown to have an anti-ischemic effect similar to that of beta-blockers.



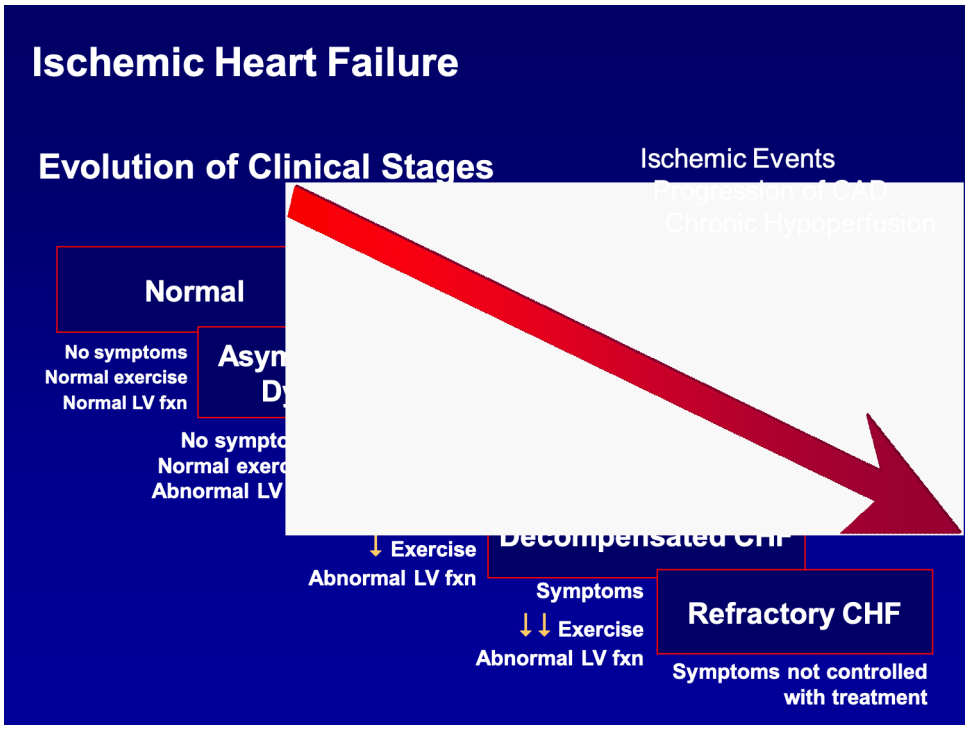
Conversely to nitrates and calcium channel blockers, Trimetazidine has been shown to improve time to 1 mm ST depression and exercise time in patients on background therapy with beta-blockers.



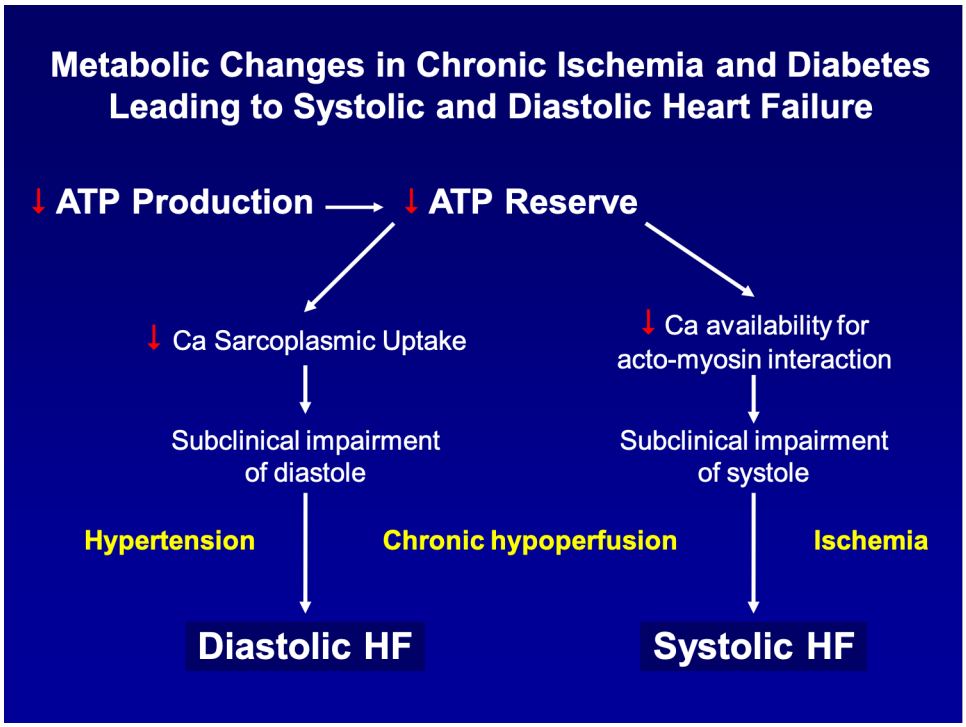
Trimetazidine has been shown to improve symptoms in patients with ischemic heart disease and in patients with resistant and recurrent angina.



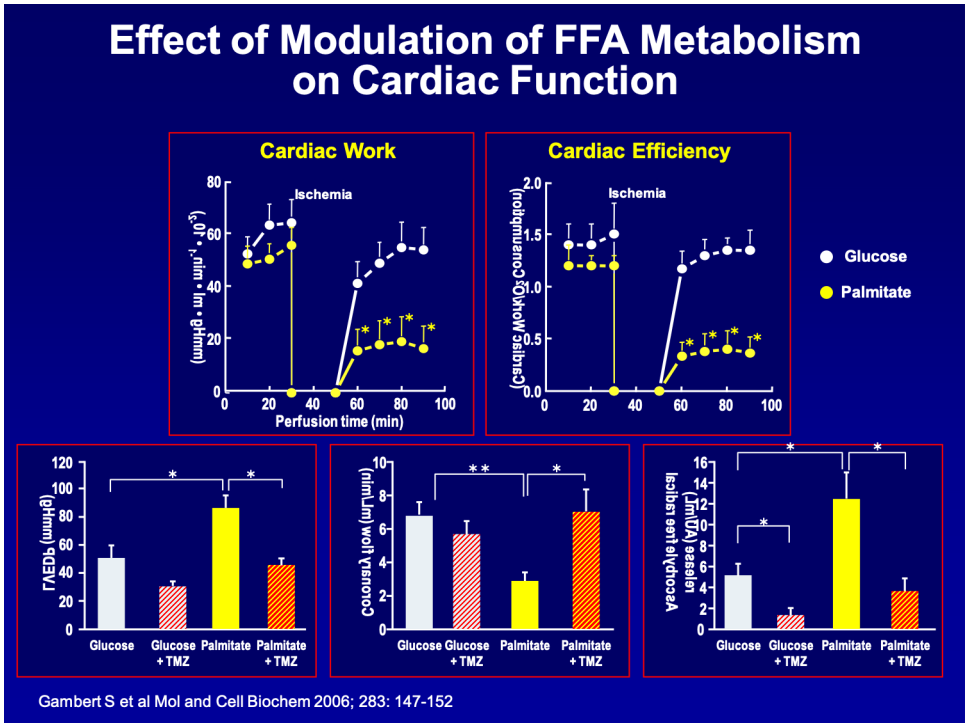
Further to the anti-ischemic effect, modulation of cardiac metabolism may represent an alternative approach to the treatment of ischemic and diabetic heart failure. Patients with ischemic heart disease and those with diabetes often develop left ventricular dysfunction because of the progression of coronary artery disease, chronic hypoperfusion and occurrence of new ischemic episodes.



The metabolic and functional effects of metabolic agents in the settings of heart failure is of particular relevance in patients with diabetes mellitus in whom glucose metabolism is impaired and myocardial metabolism is shifted towards a preferential utilization of fatty acids. Because of the preferential promotion of glucose and pyruvate oxidation,the improvement of glucose metabolism leads to an improved contractility and to an increased activity of the sodium-potassium ATPase and the calcium uptake pump of the sarcoplasmic reticulum, that are respectively responsible of left ventricular systolic depolarization and diastolic relaxation.



Studies on isolated and perfused hearts have shown that after coronary artery ligation, if the heart is perfused with fatty acids there is a modest recovery of left ventricular function while is glucose is used in the perfusate there is a prompt recovery of left ventricular function, thereby suggesting that glucose metabolism is more efficient for the recovery of left ventricular function after ischemia.



The metabolic effect of improved myocardial glucose metabolism modulation translates into a reduced total ischemic burden and into a better utilization of metabolic substrates that translates into a greater mechanical efficiency.

Intracoronary pyruvate was shown to acutely increase stroke volume and reduce pulmonary capillary wedge pressure, implying acute beneficial effects of a shift away from fatty acid metabolism in patients with heart failure. This finding drove interest in the potential beneficial effects of modifying substrate utilisation in chronic heart failure. A number of pharmacological agents have been shown to inhibit FFA utilisation in the heart, some of these agents have been tested in clinical trials.

As mentioned, Perhexiline is a reversible inhibitor of both CPT1 and CPT2 which are key enzymes involved in the transport of free fatty acids into the mitochondria. Perhexiline is used as antianginal agent, improves exercise tolerance, and ischemic treashold. Its use however is limited because of hepatotoxic effects and peripheral neuropathy. The risk of toxic effects is virtually eliminated by maintaining plasma concentrations at between 150 and 600 ng/ml, at this level the drug also remains efficacious. Perhexiline has been shown in a double-blind, randomized, placebo-controlled trial, to have shown short-term beneficial effects of in patients with ischemic or non-ischemic heart failure.

Oxfenicine is an irrevrsible inhibitor of carnitine palmitoyltransferase I (CPT1). Oxfenicine has been shown to delay development of terminal heart failure, attenuate adverse hemodynamic changes, prevent wall thinning. No human studies have been reported with use of Oxfenicine in heart failure.

Etomoxir an irreversible inhibitor of CPT1 introduced as an antidiabetic drug. In humans, a 3-month, open-label, trial in 10 patients with NYHA class II–III heart failure, etomoxir treatment in addition to standard therapy significantly improved left ventricular ejection fraction, cardiac output at peak exercise, and clinical status. Subsequently, a large randomized placebo controlled study was terminated prematurely because of the development of significant hepatotoxicity.

β-adrenoreceptor blockade improves left ventricular function and prognosis in patients with heart failure. Wallhaus et al. demonstrated that carvedilol in patients with heart failure caused a 57%

reduction in myocardial free fatty acid uptake. In another study, Al-Hesayen and colleagues showed that after 4 months of carvedilol therapy, myocardial lactate consumption was increased and myocardial uptake of free fatty acids in patients with chronic heart failure was reduced. This suggests that carvedilol therapy may cause a significant shift in myocardial substrate use from free fatty acids to glucose. The effect does not seem to be related to an ancillary property of carvedilol but seems to be related to the metabolic changes of beta blockade on cardiac metabolism and therefore shared by most beta-blockers

Trimetazidine is the metabolic agent with the largest clinical evidence in heart failure. In a double-blind, placebo-controlled trial involving 47 patients with coronary artery disease and a reduced left ventricular function, limited by angina but not by heart failure, trimetazidine therapy improved left ventricular systolic and diastolic function and quality of life. A number of other studies also demonstrated benefits with Trimetazidine. Di Napoli et al demonstrated in an 18 months, open-label study a significant improvement in left ventricular function and survival in patients with ischemic cardiomyopathy with reduced left ventricular ejection fraction. Our group demonstrated improvements in left ventricular ejection fraction among patients with diabetes and coronary heart disease, and in elderly patients with ischemic left ventricular dysfunction all with a mean left ventricular function <35%. Fragasso et al demonstrated in patients with both ischaemic and non-ischaemic cardiomyopathy increase in LVEF and NYHA class with the use of Trimetazidine.

Ranolazine has been shown to be a partial inhibitor of fatty acid β oxidation [91;92], but this has not been reliably replicated in large experimental or human studies and is not present at therapeutic doses. The exact mechanism of action of this drug is at the present largely unknown although it has been suggested that ranolazine reduces sodium entry into ischemic myocardial cells and, therefore, is thought to indirectly reduce calcium uptake via the sodium–calcium exchanger, to preserve ionic

homeostasis. The drug has some anti-anginal properties but this issue is still controversial. So far there have been no studies looking at the effects of ranolazine in humans with chronic heart failure. There are reports that the drug prolongs the QT interval on electrocardiograms. This effect raises concerns about possible complications such as torsade de pointes polymorphic ventricular tachycardia and sudden cardiac death. Therefore, the long-term safety of ranolazine needs further investigations.

Glucagon-like peptide-1 (GLP-1) is an incretin that increases myocardial glucose uptake. In a dog model of heart failure, GLP-1 improved LV function and systemic haemodynamics. In small open label study, chronic infusion of GLP-1 significantly improved left ventricular function, functional status, and quality of life in patients with severe heart failure.

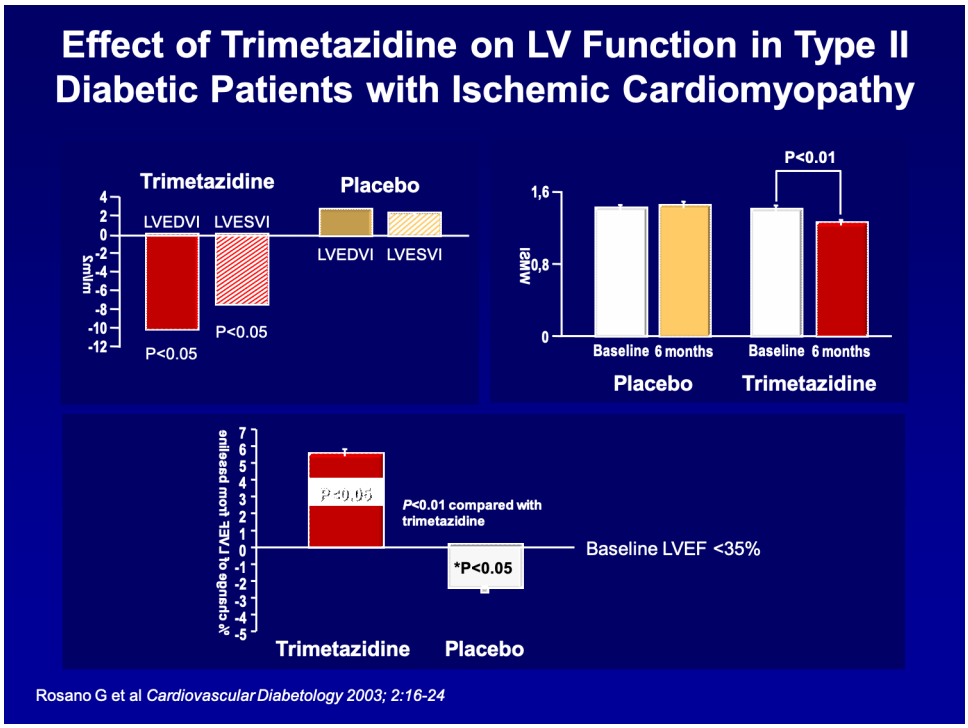
D-Ribose increases ATP production by entering the pentose phosphate pathway and bypassing rate limiting steps of glycolysis.

In a prospective, double blind, randomised, cross over design study, Omran et al showed an improvement in quality of life and diastolic function with ribose supplementation in patients with ischaemic cardiomyopathy.

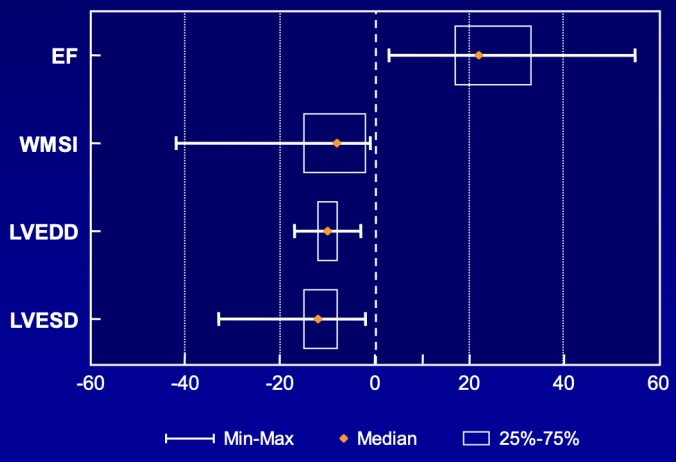
It is well known that carnitine deficiency may cause heart failure. Carnitine is an important co-factor in intermediary metabolism of the myocardium which improves utilisation of pyruvate in Krebs cycle. Studies with carnitine supplementation have shown mixed results.

Metabolic Agent	Author	Study design	No Patients	Patient Characteristics	Study duration	Outcome
Perhexiline	Lee *et al* 2005	RC PCT* Double blind	56	EF≤ 45 Non-ischemic and Ischemic CHF NYHA II-IV	2 months	LVEF $V_{o2\ max}$ Improved quality of life (QOL)
Trimetazidine	Vitale C *et al* 2004	RC PCT	47	EF< 40% Chronic stable angina NYHA I-III	6 months	↑ LVEF Better QOL Improved event free survival
Trimetazidine	Di Napoli et al 2005, 2007	Open label	61	LVEF <40% Ischeamic LV dysfunction NYHA II-IV	18 months	↑ LVEF Improved – NYHA Improved event free survival
Trimetazidine	Fragasso G *et al* 2006	Open label	55	LVEF<45% Ischaemic and Non-ishchaemic CHF NYHA II-III	13 months	↑ LVEF Improved - NYHA
Trimetazidine	Rosano G *et al* 2003 Fragasso G et al 2003	RC PCT RC PCT	86 61	EF< 40% Chronic stable angina NYHA I-III	6 months 3 months	↑ LVEF Better QOL Improved glucose tolerance
Etomoxir	Schmidt-Schweda *et al* 2000	Open label	10	LVEF<40% Dilated Cardiomyopathy NYHAII-III	3 months	↑ LVEF Increased Stroke volume during exercise
Etomoxir	Holubarsch CJ *et al* 2007	RC PCT	350	LVEF<40% Ischaemic and Non-ischaemic moderate CHF NYHA II-III	6 months	Study stopped prematurely because of hepatotoxicity.
D-Ribose	Omran *et al* 2003	RC PCT Cross over	15	Ischaemic Cardiomyopathy NYHA II-III	3 weeks	Improved functional capacity and diastolic function
L-Carnitine	Anand *et al* 1998	RC PCT Single blind	30	LVEF<40% NYHA II-III Ischaemic and non-ischaemic cardiomyopathy	4 weeks	↑ VO2 max No change in LVEF

Glucagon-like Peptide 1	Sokos *et al* 2006	Open label	12	NYHA III-IV		5 weeks	LVEF Improved QOL



Effect of Trimetazidine Elderly Patients with Ischemic Cardiomyopathy



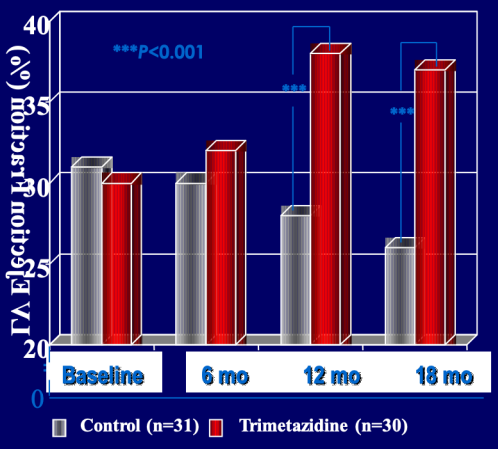
Vitale C et al. Eur Heart J 2004; 25:181 1821

Long-term Treatment with Trimetazidine Improves LV Function in Patients with ICM

61 CAD patients with dilated ICM (previous MI) and LVEF<40%

Open label design. Pts. randomized to 18-month trimetazidine (20 mg tds) added to conventional treatment, or conventional treatment alone

LV function (EF) assessed by echocardiography

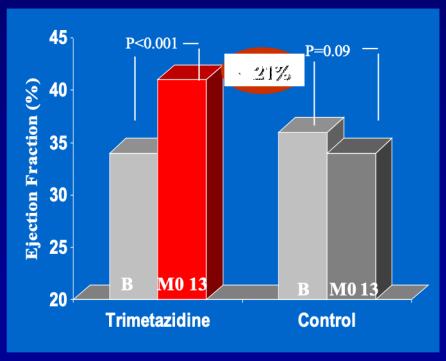


Di Napoli P, Taccardi AA, Barsotti A. Heart 2005; 91: 161-165

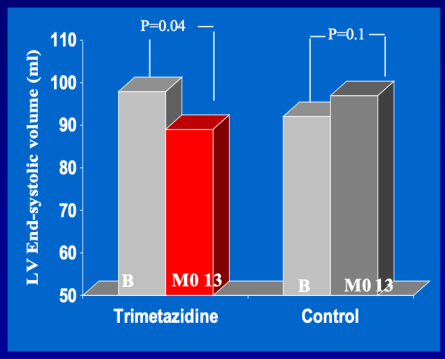
Benefits of trimetazidine in heart failure

Lor term treatment with Trimetazidine improves LV function

❖ LV Ejection Fraction



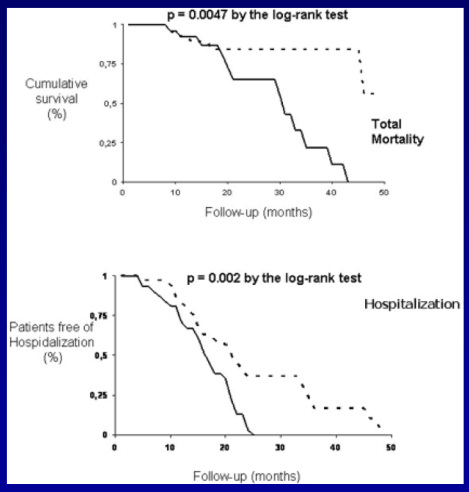
❖ LV end-systolic volume



A significant decrease in NYHA class ($p<0.0001$) has also been observed

G Fragasso, et al. JACC 2006;48;992-998

Effect of Metabolic Therapy in Heart Failure



Di Napoli et al. Circulation 2007; 116:31 334.

"The heart is more than a pump. It is also an organ that needs energy from metabolism.

A metabolic disease, ischemia, should ideally be treated by metabolic therapy"

L. Opie

Opie L. Lancet 1999;353:768–769