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## Metabolic Modulators for Chronic Cardiac Ischemia

Pirouz Parang, MD,\* Bramah Singh, MD,† and Rohit Arora, MD‡

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Many patients with ischemic heart disease continue to experience anginal symptoms despite revascularization and treatment with antianginal medications. The effectiveness of current anti-ischemic medications is limited by their hemodynamic side effects, such as hypotension and bradycardia, which result in compromised organ perfusion. In this article, we review five novel agents (ranolazine, trimetazidine, L-carnitine, ribose, and dichloroacetate) under investigation for treatment of ischemic heart disease that work by enhancing the efficiency of the myocardium, rather than decreasing its work. This new paradigm promises to eliminate these side effects.

**Key words:** ischemia, angina, coronary heart disease.

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Up to 26% of patients with coronary heart disease continue to experience ischemic symptoms despite mechanical revascularization and optimal medical anti-ischemic therapy (1). Ischemic symptoms such as angina are caused by an imbalance between oxygen delivery and oxygen requirements of the myocardium.

Revascularization by coronary artery bypass grafting or percutaneous coronary intervention increases oxygen delivery, whereas current medical therapy works by reducing the oxygen demand through decreasing cardiac work. This is done through a reduction in preload and afterload and by negative inotropism, which often leads to unacceptable side effects of hypotension, bradycardia, and organ hypoperfusion (Table 1).

A novel approach to this problem would try to decrease the heart's oxygen requirements without

affecting cardiac work, and in effect, make the heart a more efficient pump. A medication that thus increases the efficiency of the heart should have no effect on blood pressure, heart rate, or left ventricular function. In this article we review five such compounds currently under investigation: ranolazine, trimetazidine, L-carnitine, ribose, and dichloroacetate.

Myocardial cells derive energy by oxidation of both glucose and fatty acids. Fatty acid oxidation requires higher oxygen consumption to generate the same number of adenosine triphosphate (ATP) molecules. This has been called the "oxygen-wasting effect" of fatty acid metabolism (2). In normal as well as in ischemic hearts, fatty acid oxidation is the main source of energy. Excessive use of fatty acids oxidation during ischemia as a source of energy is partly responsible for injury to and contractile dysfunction of the myocardium.

The main reason for elevated rates of fatty acid oxidation during and after the period of ischemia is the dramatic increase in levels of circulating plasma fatty acids. Elevated levels of fatty acids inhibit the enzyme pyruvate dehydrogenase, which facilitates the rate-limiting step in the oxidation of glucose, the conversion of pyruvate to acetyl coenzyme A (CoA) (3). Decoupling of glycolysis from glucose oxidation results in increased lactate levels and acidosis. This further exacerbates the inefficiency, as energy in the form of ATP is directed away from contractile func-

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Table 1. Current Agents

Drug	Heart Rate	Systolic Pressure	Myocardial Contractility
$\beta$ -Blockers	↓↓	↓	↓
Nitrates	↑	↓	↔
Dihydropyridines	↑	↓↓	↔ or ↓
Diltiazem and verapamil	↓↓	↓	↔ or ↓
Metabolic modulators	↔	↔	↔ or ↑

tion toward maintaining ionic homeostasis. In addition, accumulation of long-chain fatty acid intermediates can induce diastolic dysfunction and lower the arrhythmic threshold of the ischemic ventricle (4). The dominance of fatty acid oxidation persists into the reperfusion period, which will continue to hamper cardiac function.

Dyck et al (5) demonstrated in ex-vivo studies in rat and pig hearts that inhibition of fatty acid oxidation could increase glucose oxidation in both normal and ischemic hearts. This led to a decrease in lactate production and an increase in cardiac contractility. Inhibition of fatty acid oxidation improved cardiac function during the reperfusion period as well. Promotion of glucose oxidation by inhibition of fatty acid oxidation seems to be most effective during periods of demand-induced ischemia or during postischemic reperfusion, when there is still residual tricarboxylic acid cycle activity. It is not as effective when blood flow is completely occluded (6).

## Substituted Piperazine Compounds

### Ranolazine

Although the exact molecular mechanism for its antianginal action is unclear, it appears that ranolazine acts by inhibition of fatty acid oxidation and promotion of glucose metabolism during periods of elevated free fatty acid concentration associated with myocardial ischemia.

### Human Trials

An early clinical trial by Thadani et al (7) of 319 subjects failed to demonstrate any improvement in time to ST segment depression during exercise testing or anginal frequency with ranolazine as monotherapy compared with placebo at doses of 30, 60, or 120 mg three times daily. This negative result may have been due to the low doses of the drugs used in the study.

In a study by Cocco et al (8), immediate-release ranolazine was studied against placebo in one-time doses of 10, 60, 120, or 240 mg in 104 patients who remained symptomatic despite therapy with  $\beta$ -blocker or diltiazem. Only the 240-mg dose significantly improved time to angina, exercise duration, and time to ST segment depression on stress testing done within 3 hours after the administration of ranolazine. The three other doses showed no benefit.

Rousseau et al (9) enrolled 158 patients in a double blind study using a crossover design to compare ranolazine (400 mg three times daily), atenolol (100 mg daily), and placebo. Background  $\beta$ -blocker therapy was discontinued, although 54% of subjects remained on calcium-channel blockers, 11% on nitrates, and 4% on both. Ranolazine and atenolol showed similar results in improvement in exercise duration, time to onset of angina, and time to ST segment depression. However, a significant increase occurred in the double product (heart rate x systolic blood pressure) at the end of the exercise with ranolazine, demonstrating the increased mechanical efficiency of the myocardium with ranolazine. The results from two more recent large trials, Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) and Combination Assessment of Ranolazine in Stable Angina (CARISA), using higher doses of ranolazine, have been promising.

The MARISA trial studied sustained-release ranolazine as monotherapy in 191 patients with chronic stable angina (10). All subjects had 3 months of exertional angina that responded to  $\beta$ -blockers, calcium-channel blockers, or long-acting nitrates. All antianginal medications were discontinued during the trial. Subjects with recent unstable angina, recent myocardial infarction or coronary revascularization, or New York Heart Association (NYHA) class III or IV congestive heart failure (CHF) were excluded.

After a single-blind qualifying phase, subjects were randomized to receive double-blind treatment with twice daily doses of 500, 1000, 1500 mg or placebo for 1 week according to a four-period, balanced Latin square design. At the end of each treatment period, exercise treadmill tests were done at peak and trough drug levels.

Compared with placebo, all doses showed improvement in exercise duration, time to angina, and time to ST segment depression, at both trough and peak drug levels, with a clear dose-response relationship. The 1500-mg bid dose was associated with a less than 3 beats/min decrease in resting heart rate and a 3 mm Hg decrease in resting blood pressure at peak drug levels. Dose related adverse events, mainly dizziness, nausea, asthenia, and constipation occurred substantially higher at this dose. With the 500-mg bid dosing, the overall adverse event rate was similar to placebo. The QTc interval increased by 6, 7, and 11 milliseconds at trough and 5, 6, and 14 milliseconds at peak with the 500, 1000, and 1500-mg bid dosing, respectively. The beneficial effects and side-effect profile of the drug were consistent after subgroup analyses by history of diabetes mellitus, history of heart failure, gender, and age.

The CARISA trial studied 823 subjects who were randomized to receive ranolazine (750 mg, 1000 mg) or placebo bid in addition to background antianginal therapy with 50 mg atenolol, 180 mg long-acting diltiazem or 5 mg amlodipine once a day (1). All other antianginal drugs were withdrawn at least 5 days before the first qualifying exercise test.

Inclusion criteria were coronary heart disease, 3-month history of exertional angina, ischemic ST segment depression of at least 1 mm, and limited exercise capacity on treadmill testing. Patients with acute coronary syndrome or revascularization during the previous 2 months, NYHA class III or IV CHF, or those subjects with left bundle branch block, digoxin therapy, or resting ST segment depression that prevented satisfactory interpretation of exercise electrocardiogram were excluded.

At peak and trough levels, ranolazine increased treadmill exercise duration. The frequency of angina attacks and nitroglycerin consumption was significantly reduced with ranolazine. There were small but statistically significant drops in heart rate and blood pressure. Adverse events were reported in 26.4%, 31.2%, and 32.7% of the subjects taking placebo, and 750 and 1000 mg bid, respectively. QTc interval increased over placebo by 6.1 milliseconds and 9.2 milliseconds with the 750 and 1000-mg bid-dosing, respectively, with no reported cases of torsade de pointes.

Ranolazine is being reviewed by the US Food and Drug Administration (FDA) under a New Drug Application filed by CV Therapeutics, Palo Alto, CA.

### Trimetazidine

Trimetazidine is a metabolic agent without any negative inotropic or vasodilatory properties. The molecular mechanism of action of trimetazidine remains unclear.

### Animal Studies

In research by Kantor et al (11) on isolated working rat hearts, trimetazidine reduced the rate of fatty acid oxidation and increased glucose oxidation by inhibition of the long-chain 3-ketoacyl coenzyme A thiolase (LC 3-KAT) enzyme. These findings were disputed by McInnes et al (12), whose experiments did not show any inhibition of LC 3-KAT by trimetazidine. Lopaschuk et al (13) later confirmed the Kantor group's findings and hypothesized that the McInnes group's negative results may have been due to high concentrations of substrate used.

### Human Trials

In a double-blind study of 50 subjects, Manchanda (14) demonstrated improvement in time to 1-mm ST depression, Duke treadmill score, and frequency of angina in patients taking trimetazidine compared with placebo. In the Trimetazidine in Poland (TRIMPOL II) study, 426 patients with stable angina were randomized to receive trimetazidine or placebo in addition to metoprolol (15). There were increases in time to ST segment depression in exercise testing, exercise workload, and decreases in nitrate consumption and angina frequency.

Marzilli et al (16) published a meta-analysis of 12 randomized, double-blind trials evaluating trimetazidine conducted between 1985 and 2001. The study population in the trials ranged from 21 to 347. In all, 811 patients were studied in the 12 trials. Trimetazidine was effective in lowering the frequency of angina attacks compared with placebo. The statistical significance was lost when the drug was compared with another antianginal medication. Similarly, trimetazidine was found to significantly improve time to 1-mm ST depression when compared with placebo, but there was no statistically significant difference compared with another agent. There was no significant improvement in exercise duration, but there was a trend compared with placebo ( $P = .06$ ).

This meta-analysis reported fewer adverse events for trimetazidine compared with nifedipine, metoprolol, or propranolol. Most side effects were mild and

related to the gastrointestinal tract. The safety profile of this drug remains unknown, since no dose-response trials have been published.

Fragasso et al (17), having previously shown that heparin may decrease the ischemic threshold in patients with coronary artery disease—probably through an increase in fatty acid oxidation—conducted a trial to investigate whether this effect can be reversed with trimetazidine. In the four phases of the study, 9 patients received either intravenous (IV) heparin or placebo (IV saline) and oral trimetazidine or a placebo pill. Exercise testing was performed during each stage. Heparin caused a worsening of time to 1-mm ST segment depression and recovery time. When trimetazidine was given before the heparin infusion, these readings were similar to those obtained with placebo infusion.

## Other Compounds

### L-carnitine

L-carnitine is a naturally occurring amino acid essential for the transport of fatty acids into the mitochondria. Carnitine is involved in oxidation of long-chain fatty acids and stabilization of cellular membranes and is also a free-radical scavenger. It is synthesized in the liver and kidneys, but its plasma concentrations will drop during dietary deficiency. Since skeletal and cardiac muscle use fatty acids as main source of energy, carnitine deficiency mainly manifests as dysfunction of the above tissues. Carnitine depletion can also cause hypoglycemia, hyperammonemia, hypoketone-mia, coma, seizures, and developmental disorders (18).

Cardiac muscle contains very high levels of carnitine compared with other tissues. Myocardial ischemia has been shown to deplete carnitine levels in the myocardium. When combined with elevated levels of fatty acids during ischemia, this leads to elevation of toxic metabolites of fatty acid esterification. It has been suggested that depletion of free L-carnitine in the ischemic myocardium can impair the electrical and contractile activities of the heart.

In rats, the administration of L-carnitine has been shown to attenuate the depletion of endogenous L-carnitine and improve the recovery of the ischemic myocardium. It has also been shown to improve cardiac function in rats with ventricular hypertrophy and in rats after myocardial infarction. Carnitine may make cardiomyocytes more resistant to free radicals. Another proposed mechanism is through shifting the metabolism from fatty acid oxidation to glucose oxi-

ation. Propionyl L-carnitine (PLC) is a carnitine derivative that may have enhanced beneficial effects compared with carnitine.

### Animal Studies

Sethi et al (19) treated rats with ligated left coronary arteries and a control group with sham ligations with 4 weeks of PLC. Treatment was started 3 weeks after the ligation, since it has been shown that in rats, myocardial infarcts are fully healed after this period. The rats treated with PLC showed lower body weight gain (attributed to CHF) and lower weight of the heart (secondary to hypertrophy). The treated animals also had significantly lower left ventricular end-diastolic pressure.

Felix et al (20) showed that the addition of PLC to the drinking water of diabetic rats improved cardiac function both at baseline and after a period of no-flow ischemia. This benefit was not observed in the control group of nondiabetic rats.

### Human Trials

Iliceto et al (21) studied the benefits of carnitine in patients presenting with a first acute myocardial infarction in the L-Carnitine Ecocardiografia Digitalizzata Infarto Miocardico (CEDIM) trial in which 239 patients received carnitine or placebo within 24 hours of onset of chest pain. This was continued for 1 month. At 12 months, the patients treated with carnitine had significantly lower left ventricular end-diastolic and end-systolic pressures. Carnitine-treated patients also had less mortality from heart failure, though the difference was not statistically significant.

Singh et al (22) compared administration of carnitine with placebo in 101 patients with suspected myocardial infarction. Significant improvements were seen in infarct size (as assessed by cardiac enzymes and electrocardiogram), angina, NYHA class III or IV CHF, left ventricular enlargement, arrhythmias, and total cardiac events, including cardiac deaths and non-fatal myocardial infarctions.

Iyer et al (23) examined the efficacy of oral carnitine vs placebo in 47 patients with chronic stable angina in improving exercise tolerance. There was no improvement in time to ST depression, ST score, or rate-pressure product. The carnitine-treated group demonstrated significant improvements in exercise duration and time needed for ST changes to return to baseline.

### Ribose

Ribose is a pentose sugar that has been shown in numerous animal experiments to enhance ATP pro-

duction and improve cardiac function. Ribose can enhance metabolism by entering the pentose phosphate pathway and bypassing the rate limiting enzymes of glucose-6-phosphate dehydrogenase and 6-phosphogluconate-dehydrogenase.

### Human Trials

Pliml et al (24) studied 20 male patients with documented severe coronary artery disease. After an initial treadmill test, the subjects whose stress test showed reproducibility were randomized to receive four daily doses of ribose vs placebo. On day 5, the treadmill exercise test was repeated. The ribose-treated group showed significant improvement in time to ST segment depression and time to moderate angina. These changes were not significant in the placebo group.

Omran et al (25) studied the benefits of ribose in 15 patients with stable chronic coronary disease and NYHA class II or III CHF. Patients were given ribose or placebo (dextrose) for a 3-week treatment period. After a 1-week washout period, the alternative treatment was administered for another 3 weeks. The investigators reported significant improvements in quality of life assessed with a questionnaire and functional capacity assessed by using an exercise ergometer. Peak exercise capacity was not affected, however.

Patients were also evaluated echocardiographically before and after the treatment periods. No difference was found in left ventricular volume, stroke volume, or ejection fraction. Ribose treatment, however, resulted in significant deceleration of the E-wave, with significantly smaller left atrial volume and higher left atrial contribution of ventricular filling. The authors hypothesized that during ATP deficiency, calcium may bind to troponin longer during diastole. Treatment with ribose hence improves diastolic relaxation by restoring ATP levels. No adverse events have been reported with ribose and it seems to have no effect on hemodynamics (24).

### Dichloroacetate

Dichloroacetate is another investigational agent that promotes aerobic oxidation of carbohydrates over fatty acids. It does so by activation of the pyruvate dehydrogenase complex (PDC), a group of enzymes at the inner mitochondrial membrane. Pyruvate dehydrogenase is inactivated when phosphorylated by pyruvate dehydrogenase kinase. Dichloroacetate increases the activity of PDC by inhibiting pyruvate dehydrogenase kinase. Glucose is metabolized to pyruvate, which under aerobic condition is oxidized to acetyl CoA by the PDC. This is the rate-limiting reaction in the oxidation of glucose; therefore, dichloroacetate

can stimulate the rate-limiting step in the oxidation of glucose. Fatty acid oxidation is inhibited by increased levels of malonyl-Co A (26).

### In Vitro and Animal Studies

Barak et al (27) used <sup>13</sup>C-nuclear magnetic resonance spectroscopy to study the relative contribution of fatty acids on one hand and pyruvate and lactate on the other to the production of acetyl-CoA used in energy production. Administration of dichloroacetate significantly increased the relative contribution of lactate and pyruvate to the production of acetyl-CoA. Ischemic hearts treated with dichloroacetate also demonstrated significantly improved rate-pressure products.

In experiments on isolated rat hearts, the administration of dichloroacetate through the perfusate after 30 minutes of no-flow global ischemia improved the rate and magnitude of left ventricular recovery. In an experiment in intact dogs, administration of dichloroacetate before partial occlusion of the left anterior descending (LAD) coronary artery improved myocardial pH, ATP and lactate levels. In another experiment, dichloroacetate was administered to open-chest dogs, before or during complete occlusion of the LAD. Dichloroacetate-treated dogs had smaller rises in their ST segments.

Wambolt et al (28) studied ex-vivo administration of dichloroacetate to hearts from a group of rats with pressure-overload cardiac hypertrophy. A control group was studied that did not have hypertrophied hearts. The excised hearts were subjected to 20 minutes of global no-flow ischemia followed by reperfusion. Half the hearts received dichloroacetate in the reperfusion perfusate, while the other half did not. Mechanical function of the hearts was assessed by the measurement of peak systolic pressure, rate-pressure product, cardiac output, hydraulic work, and coronary flow. In the ischemic group, all of these parameters—except for the peak systolic pressure in hypertrophic hearts—showed significant improvement with administration of dichloroacetate. In the control, nonischemic group, the hypertrophied hearts had similar improvements with the administration of dichloroacetate.

Using a model of transient myocardial ischemia in live pigs, Kudej et al (26) demonstrated that the administration of dichloroacetate shortly after reperfusion significantly reduced the length of the period of myocardial stunning.

### Human Studies

In an experiment by Wargovich (29) in human subjects with coronary artery disease, 9 such patients undergoing catheterization were given intravenous

dichloroacetate. It improved left ventricular stroke volume and decreased systemic vascular resistance and myocardial efficiency index. No changes were seen in left ventricular end-diastolic pressure, left ventricular  $dP/dt_{max}$ , coronary sinus flow, coronary resistance, or myocardial oxygen consumption.

### Discussion

Through biochemically distinct mechanisms, these agents appear to improve myocardial efficiency and relieve ischemia without producing the dose-limiting side effects of agents currently in use. Current data looks promising, but further research is needed to address the following issues:

1. Except for the CARISA, and MARISA trials evaluating ranolazine, and the TRIMPOL trial evaluating trimetazidine, currently available data come from small studies. There are no long-term efficacy or safety data with any of the agents. The clinical significance of the QTc prolongation seen with ranolazine and its arrhythmogenic potential cannot yet be adequately assessed. Event rates for sudden cardiac death and torsade de pointes may be so low that an increased risk cannot be ruled out with the small sample sizes and short follow-up periods of the current studies.
2. Only intermediate end points (exercise duration, time to angina, etc) were studied. Major clinical end points such as death or myocardial infarction were not evaluated.
3. There is no consistent use of two stress tests at baseline to demonstrate stable baseline exercise duration and ischemic threshold.
4. There is no clear justification on the choice of medications and doses (ie, diltiazem, 240 mg) against which the new agents have been tested.

Nevertheless, this represents an exciting and potentially revolutionary new paradigm for the treatment of chronic myocardial ischemia that deserves to be rigorously studied.

### References

1. Chaitman BR, Pepine CJ, Parker JO, et al. Combination Assessment of Ranolazine In Stable Angina (CARISA) Investigators. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina. *JAMA* 291:309–316, 2004
2. Hüter JF, Piper HM, Spieckermann PG. Effect of fatty acid oxidation on efficiency of energy production in rat heart. *Am J Physiol* 249(4 Pt 2):H723–728, 1985
3. Anderson JR, Khou S, Nawarkas JJ. Ranolazine. A potential new treatment for chronic stable angina. *Heart Disease* 3:264–269, 2001
4. Leong L, Horowitz J, Frenneaux M. Metabolic manipulation in ischemic heart disease, a novel approach to treatment. *Eur Heart J* 25:634–641, 2004
5. Dyck J, Cheng J-F, Stanley W, et al. Malonyl coenzyme A decarboxylase inhibition protects the ischemic heart by inhibiting fatty acid oxidation and stimulating glucose oxidation. *Circ Res* 94:e78–e84, 2004
6. McCormack JG, Stanley WC, Wolff AA. Ranolazine: A novel metabolic modulator for the treatment of angina. *Gen Pharmac* 30:639–645, 1998
7. Thadani U, Ezckowitz M, Fenney L, et al. Double blind efficacy and safety study of a novel anti-ischemic agent, ranolazine, versus placebo in patients with chronic stable angina pectoris. *Circulation* 90:726–734, 1994
8. Cocco G, Rousseau MF, Bouvy T, et al. Effects of a new metabolic modulator, ranolazine, on exercise tolerance in angina pectoris patients treated with beta-blocker or diltiazem. *J Cardiovasc Pharmac* 20:131–138, 1992
9. Rousseau MF, Visser FF, Bax JJ, et al. Ranolazine: Anti-anginal therapy with a novel mechanism: Controlled comparison versus atenolol. *Eur Heart J* 15:95, 1994
10. Chaitman BR, Skettino SL, Parker JO, et al. MARISA Investigators. Anti-ischemic effects and long term survival during ranolazine monotherapy in patients with chronic severe angina. *J Am Coll Cardiol* 43:1375–1382, 2004
11. Kantor PF, Lucien A, Kozak R, et al. The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. *Circ Res* 86:580–588, 2000
12. MacInnes A, Fairman DA, Binding P, et al. The anti-anginal agent trimetazidine does not exert its functional benefit via inhibition of mitochondrial long-chain 3-ketoacyl coenzyme a thiolase. *Circ Res* 93:e26–e32, 2003
13. Lopaschuk GD, Barr R, Thomas PD, et al. Beneficial effects of trimetazidine in ex vivo working ischemic hearts are due to a stimulation of glucose oxidation secondary to inhibition of long-chain 3-ketoacyl coenzyme A thiolase. *Circ Res* 93:e33–e37, 2003
14. Manchanda SC. Treatment of stable angina with low dose diltiazem in combination with the metabolic agent trimetazidine. *Int J Cardiol* 88:83–89, 2003
15. Szwed H, Sadowski Z, Elikowski W, et al. Combination treatment in stable effort angina using trimetazidine and metoprolol: Results of a randomized, double-blind, multicentre study (TRIMPOL II) TRImetazidine in POLand. *Eur Heart J* 22:2267–2274, 2001
16. Marzilli M, Klein W. Efficacy of tolerability of trimetazidine in stable angina: A meta-analysis of randomized, double-blind, controlled trials. *Coron Artery Dis* 14:171–179, 2003
17. Fragasso G, Piatti PM, Monti L, et al. Acute effects of heparin administration on the ischemic threshold of patients with coronary artery disease. Evaluation of the

- protective role of the metabolic modulator trimetazidine. *J Am Coll Cardiol* 39:413–419, 2002
18. Lango R, Smolenski RT, Narkiewicz M, et al. Influence of L-carnitine and its derivatives on myocardial metabolism and function in ischemic heart disease and during cardiopulmonary bypass. *Cardiovasc Res* 51:21–29, 2001
  19. Sethi R, Dhalla KS, Ganguly PK, et al. Beneficial effects of propionyl L-carnitine on sarcolemmal changes in congestive heart failure due to myocardial infarction. *Cardiovasc Res* 42:607–615, 1999
  20. Felix C, Gillis M, Driedzic WR, et al. Effects of propionyl L-carnitine on isolated mitochondrial function in the reperfused diabetic rat hearts. *Diabetes Clin Pract* 53:17–24, 2001
  21. Iliceto S, Scutrinio D, Bruzzi P, et al. Effects of L-carnitine administration on left ventricular remodeling after acute anterior myocardial infarction: The L-Carnitine Ecocardiografia Digitalizzata Infarto Miocardico (CEDIM) trial. *J Am Coll Cardiol* 26:380–387, 1995
  22. Singh RB, Niaz MA, Agarwal P, et al. A randomized, double-blind, placebo-controlled trial of L-carnitine in suspected myocardial infarction. *Postgrad Med J* 72:45–50, 1996
  23. Iyer RN, Khan AA, Gupta A, et al. L-carnitine moderately improves the exercise tolerance in chronic stable angina. *J Assoc Physicians India* 48:1050–1052, 2000
  24. Pliml W, Von Arnim T, Stablein K, et al. Effects of ribose on exercise-induced ischemia in stable coronary artery disease. *Lancet* 340:507–510, 1992
  25. Omran H, Illien S, MacCarter D, et al. D-ribose improves diastolic function and quality of life in congestive heart failure patients: A prospective feasibility study. *Eur J Heart Fail* 5:615–619, 2003
  26. Kudej R, White L, Kudej A, et al. Brief increase in carbohydrate oxidation after reperfusion reverses myocardial stunning in conscious pigs. *Circulation* 106:2836–2841, 2002
  27. Barak C, Reed M, Maniscalco S, et al. Effects of dichloroacetate on mechanical recovery and oxidation of physiologic substrates after ischemia and reperfusion in the isolated heart. *J Cardiovasc Pharmacol* 31:336–344, 1998
  28. Wambolt R, Lopaschuk G, Browney R, et al. Dichloroacetate improves postischemic function of hypertrophied rat hearts. *J Am Coll Cardiol* 36:1378–1385, 2000
  29. Wargovich TJ, MacDonald RG, Hill JA, et al. Myocardial metabolic and hemodynamic effects of dichloroacetate in coronary artery disease. *Am J Cardiol* 61:65–70, 1988