Invited review

Metabolic management of diabetic patients with ischaemic heart disease

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Abstract

Diabetic patients with ischaemic heart disease have a greater rate of myocardial ischaemia, often silent, compared with patients without diabetes. Furthermore, patients with coronary artery disease (CAD) and diabetes have altered myocardial metabolism and accelerated and diffuse atherogenesis with involvement of distal coronary segments that causes chronic hypoperfusion and hibernation. Therefore, in patients with diabetes and CAD, the ischaemic metabolic changes are heightened by the metabolic changes related to diabetes. Metabolic changes during diabetes and myocardial ischaemia include an increase in free fatty acid (FFA) concentrations with increased skeletal muscle and myocardial FFA uptake and oxidation, and reduced utilization of glucose as a source of energy during stress. This contributes to the increased susceptibility of diabetic hearts to myocardial ischaemia and to a greater decrease of myocardial performance for a given amount of ischaemia compared with non-diabetic hearts. The metabolic approach, including strict glycaemic control and inhibition of FFA oxidation, aims to obtain an improvement in myocardial metabolism, relief of ischaemia and recovery of left ventricular function. The inhibition of FFA oxidation with trimetazidine improves cardiac metabolism at rest, increases cardiac resistance to ischaemia, and therefore reduces the decrease of LV function caused by chronic hypoperfusion and episodes of myocardial ischaemia in patients with and without diabetes. Thus, modulation of myocardial FFA metabolism should be the key target for metabolic interventions in patients with CAD with and without diabetes. In patients with diabetes, the effects of modulation of FFA metabolism should be even greater than those observed in patients without diabetes. Because of its effect on cardiac metabolism at rest and its effects on myocardial ischaemia and LV function, metabolic agents should always be considered for the treatment of patients with diabetes with CAD with or without LV dysfunction.

Key words: myocardial metabolism, ischaemia, trimetazidine, oxidation, diabetes.

Introduction

Patients with diabetes form a substantial proportion of patients with coronary artery disease (CAD) [1]. In some respects, clinical presentation, management and outcome of CAD patients with diabetes are different from non-diabetic patients.

Diabetic patients with CAD have a lower incidence of chest pain and higher incidence of silent ischaemia than non-diabetic. Up to 30% of patients with diabetes and CAD have silent episodes of myocardial ischaemia either during provocative tests (exercise testing, cardiac stress imaging) or during daily life (ambulatory electrocardiographic monitoring) [2, 3].

Although atherosclerotic plaques appear to be morphologically similar in patients with or without diabetes, pathologic studies have demonstrated that coronary arteries in patients with diabetes and CAD show diffuse disease, in contrast to the more localized involvement often seen in the absence of diabetes [4].

From a prognostic point of view, the combination of diabetes and CAD is associated with a higher rate of cardiac events and a poorer prognosis. Evidence for this includes increased risk of recurrent infarction. In the study of Haffner et al. [5], the 7-year risk of myocardial infarction among those with diabetes with and without a prior myocardial infarction at baseline was 45 and 20.2%, respectively. The corresponding values for non-diabetic subjects were 18.8 and 3.5%. Diabetic patients have also increased morbidity and mortality associated with myocardial infarction, as well as a higher risk of developing congestive heart failure. In the FINMONICA project [6], the 1-year mortality rate after a first myocardial infarction among diabetic patients was 44.2% for men and 36.9% for women, compared with 32.6 and 20.2% for non-diabetic men and women, respectively.

Several pathophysiological factors contribute to accelerate the atherosclerotic process and predispose to higher rates of CAD in diabetic subjects: microvascular dysfunction [7], decreased fibrinolytic activity [8], elevated spontaneous platelet aggregability [9], atherogenic lipoprotein profile [10], autonomic dysfunction [11] and possible coexisting diabetic cardiomyopathy [12].

Furthermore, the control of vascular tone is altered at an early stage in diabetes with a reduced vasodilatory response to different stimuli that is strongly related to glycaemic control [13].

High glucose levels seem to play a predominant role in pathogenesis of diabetic cardiovascular complications and in particular in the onset of vascular damage. This has been convincingly demonstrated by both the Diabetes Control and Complication Trials (DCCT) [14] and the UK Prospective Diabetes Study (UKPDS) [15].

The relationship between fasting hyperglycaemia and CAD has been addressed in several epidemiologic studies such as the Chicago Heart Association Detection Project [16], Tecumseh Study [17] and Paris Prospective Study [18]. These studies have shown that asymptomatic hyperglycaemia is associated with increased mortality from CAD. In the DECODE study [19], the 2-h post-glucose glucose concentration was more clearly related to cardiovascular mortality than fasting blood glucose. This may be due to microvascular dysfunction related to high values of postprandial glucose and by the higher sensitivity of oral glucose tolerance test in identifying patients with diabetes compared to fasting glucose.

Hyperglycaemia induces vascular damage mainly through increased production of free radicals with a reduction in NO availability [7, 20]. Generation of oxygen-derived free radicals is promoted by several mechanisms including autoxidation, nonenzymatic glycation of proteins, increased de novo synthesis of diacylglycerol from glycolytic intermediates and subsequent activation of phosphokinase [21].

Another well known factor involved in atherosclerosis progression and endothelial dysfunction in diabetes is insulin resistance [22]. Hyperinsulinaemia can directly contribute to vascular damage promoting migration of monocytes and smooth muscle cells into the arterial wall [23].

Energy metabolism of the heart during ischaemia and diabetes

Under aerobic conditions the predominant substrate used by the normal adult human heart is free fatty acids (FFA), accounting for 60-90% of the energy generated [24]. Long-chain fatty acids (LCFA) are the major component of FFA utilisation. Following cellular uptake, LCFA entry into the mitochondria is facilitated by the enzymes carnitine palmitoyl-transferase (CPT) I and II. Beta-oxidation then occurs, which yields acetyl-CoA. Acetyl-CoA enters the tricarboxylic acid cycle and eventually leads to the formation of ATP, which is critical for myocardial contraction and relaxation.

Carbohydrate metabolism, on the other hand, contributes only about 10-40% of energy generated by the healthy adult human heart at rest [25]. The glucose taken up by cardiomyocytes is stored as glycogen or converted into pyruvate by glycolysis. Pyruvate is then oxidised within the mitochondria by pyruvate dehydrogenase into acetyl CoA.

All metabolic adaptive mechanisms during ischaemia, whether physiological or pharmaceutical, regulate energy metabolism by shifting substrate use towards glucose metabolism. The energetic advantages of incremental glucose utilisation arise from the fact that though fatty acid oxidation yields more ATP than glycolysis in aerobic conditions, this is at the expense of greater oxygen consumption. Fatty acids require approximately 10-15% more oxygen to generate an equivalent amount of ATP compared to glucose [26]. During subtotal ischaemia, the myocardium continues to derive a large proportion of its energy from oxidative metabolism. In moderate-to-severe ischaemia, there is increased utilisation by the myocardium of glucose as a substrate for energy production [27, 28]. Nevertheless, FFA oxidation continues to be the predominant substrate in the ischaemic heart [26, 29].

High levels of FFA uptake and catabolism during the ischaemic period require a higher oxygen expenditure to generate energy than glucose metabolism and may have detrimental effects on the myocardium [30]. High rates of FFA oxidation suppress glucose oxidation through a direct inhibitory

action on pyruvate dehydrogenase [31], and increase lactate and proton accumulation in ischaemic cells [32], leading to a reduction in the contractile function of myocardial segments. Accumulation of LCFA intermediates during beta-oxidation has previously been shown to reduce the ventricular arrhythmia threshold [33] and induce diastolic dysfunction [34] during ischaemia.

In patients with diabetes and CAD, the metabolic changes occurring as a consequence of the mismatch between blood supply and cardiac metabolic requirements are heightened by the metabolic changes occurring with diabetes. Diabetes causes a switch of the energy metabolism from carbohydrate oxidation to free FFA and ketone oxidation [35]. In diabetes the reduced glucose uptake that is coupled with preferential FFA oxidation occurs as a consequence of inadequate insulin receptor signalling related to either a state of insulin resistance or decreased insulin levels. Increased FFA concentrations and increased skeletal muscle and myocardial FFA uptake and oxidation have detrimental consequences on cardiac function and particularly on the ischaemic heart. The presence of myocardial insulin resistance has been demonstrated in patients with diabetes, suggesting that even early stages of altered glycaemic control may affect myocardial metabolism and predispose to diabetic cardiomyopathy [36-39]. The lack of insulin and the state of insulin resistance may influence cardiac function through several different mechanisms, such as decreased glucose transport and carbohydrate oxidation, increase in FFA use, decrease in sarcolemmal calcium transport, and alterations in myofibrillary regulatory contractile proteins. In the diabetic heart, myocardial glucose uptake, availability and use are blunted when fasting and after insulin stimulation [35, 40].

The increased uptake and use of FFA is maximal during stress and ischaemia and is a major contributor to the increased susceptibility of the diabetic heart to myocardial ischaemia and to a greater decrease in myocardial performance for a given amount of ischaemia compared with the non-diabetic heart [41-44].

Moreover, in the diabetic heart, the preferential increased uptake of FFA during stress or ischaemia causes not only diminished energy production, but also a parallel increase in intermediate metabolic products that are toxic for the cells, especially during ischaemia or increased workload [44]. This can contribute to both the development of contractile dysfunction and to increased sensitivity of the heart to injury during ischaemia [45].

Treatment of diabetes in patients with CAD

Treatment of diabetes and above all control of glycaemia is a standard recommendation for individuals who have diabetes with CAD. Several studies have shown that intensive glycaemic control is highly effective in preventing and retarding microvascular and, to a lesser degree, macrovascular complications in both type I and type II DM. The DCCT provided definite evidence of a major reduction in chronic microvascular complications among a group of type I diabetic patients with tight glycaemic control and suggested a potential beneficial effect of this strategy on macrovascular disease [14]. Tight glycaemic control reduced major macrovascular events by one-half in diabetics compared with conventionally treated patients [46].

The randomized United Kingdom Prospective Diabetes Study (UKPDS) [15] has reported that, over 10 years of follow-up, intensive glycaemic control by either insulin or sulphonylureas significantly reduced (by 25%) the risk of microvascular complications in NIRDM patients. A similar reduction was observed in diet-treated obese NIRDM patients taking metformin [47]. In addition, a recent retrospective study has reported that optimal glycaemic control in diabetic patients can favourably influence major cardiac events following PTCA [48].

The role of reducing glycaemia has been emphasized in the early stage after myocardial infarction. According to ESC guidelines [49], glucose control by means of insulin should be immediately initiated in diabetic patients admitted for acute MI with significantly elevated blood glucose levels in order to reach normoglycaemia as soon as possible. This goal in the intensive care units has been reached by glucose-insulin-potassium (GIK) infusion. GIK works by stimulating glucose uptake and glycogen synthesis while inhibiting fatty acid release from adipocytes. In the study by Rackley et al. [50], GIK induced an increase in the respiratory quotient, demonstrating a shift in energy substrate metabolism from lipids to carbohydrate. Related factors may also come into play, such as improved sodium and calcium homeostasis.

The DIGAMI 1 study [51] recruited 620 diabetic patients with acute MI to be randomly assigned to serve as a control group or to a group receiving intensive insulin treatment initiated by insulin-glucose infusion during the first 24 h post-MI. In the intensively treated group 1-year mortality was reduced by 30%. In a long-term follow-up over an average of 3.4 years, there was an 11% absolute mortality reduction in the intensively treated group.

The DIGAMI 2 trial [52] enrolled 1253 diabetic patients with acute MI and compared three management protocols: acute insulin-glucose infusion followed by insulin-based long-term glucose control, insulin-glucose infusion followed by standard glucose control, and routine metabolic management according to local practice. The study did not show any benefit on survival of long-term intensive insulin treatment.

Moreover, initiating treatment with an insulin-glucose infusion was not superior to standard management. However, the three glucose management strategies did not result in significantly different long-term glucose control and target glucose levels were not reached in the intensive insulin treated group.

A meta-analysis of several studies on GIK therapy in acute MI including 1932 patients suggested a proportional mortality reduction of 28% with 49 lives saved per 1000 patients treated with GIK [53].

Treatment of ischaemia in CAD patients with diabetes

According to the classic pathogenetic view, myocardial ischaemia is caused by an imbalance between myocardial metabolic demands and myocardial blood supply. Such an imbalance may result either from an increase in cardiac work that is not accompanied by a parallel increase in coronary blood flow, or from a primary reduction in coronary blood flow. The conventional management of stable angina focuses on reducing myocardial demand by means of drugs that act on "haemodynamic" parameters.

Beta-blockers and calcium channel antagonists reduce cardiac work and myocardial oxygen consumption, reducing heart rate, blood pressure and myocardial contractility. Nitrates lower coronary smooth muscle tone, dilate coronary epicardial vessels and prevent coronary vasospasm.

The "haemodynamic" drugs improve symptoms and quality of life in many patients with angina pectoris but they do not have an additive anti-ischaemic effect when given in combination. Also adverse effects are often observed and may limit the usefulness of haemodynamic agents. The most common dose-limiting adverse effects are cold peripheries, weakness and "heavy legs" feeling in patients receiving beta-blockers, fluid retention in those receiving calcium antagonists, and headaches in individuals receiving oral nitrates. To circumvent these effects, suboptimal combination treatment is often used.

An alternative strategy is to address the metabolic causes or consequences of ischaemia. The "Metabolic" anti-anginal therapies induce a shift from FFA towards predominantly glucose utilisation by the myocardium to increase ATP generation per unit oxygen consumption.

The use of metabolic agents in CAD patients with diabetes represents a logical approach to their treatment, given the mechanism of action of these agents, because patients with diabetes exhibit reduced glucose uptake and utilization, and an increased uptake and utilization of FFAs [35]. Moreover, patients with diabetes are more metabolically vulnerable to ischaemia than non-diabetics.

Perhexiline

Perhexiline is the oldest anti-ischaemic drug with metabolic effects. It was frequently prescribed as an anti-anginal agent in the 1970s. Early randomised controlled trials in patients with coronary artery disease demonstrated that perhexiline markedly relieved symptoms of angina, improved exercise tolerance and increased the workload needed to induce ischaemia when used as monotherapy [54]. More recently, randomised controlled trials have demonstrated that perhexiline exerts marked, incremental anti-anginal effects in patients receiving beta-blockers or even "triple" prophylactic anti-anginal therapy [55].

Perhexiline is not negatively inotropic and does not alter systemic vascular resistance to a significant degree at plasma levels that are within therapeutic range. It acts through the inhibition of palmitoyl camitine transferase [56].

Despite its potential benefits, perhexiline use declined dramatically in the early 1980s following reports of hepatotoxicity [57] and peripheral neuropathy [58]. 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 [59].

Trimetazidine

Trimetazidine (TMZ) was developed and registered as anti-anginal in the late 1980s. Since then TMZ has been marketed in Europe, Asia and Latin America as a safe cellular anti-ischaemic drug devoid of haemodynamic effects.

The mechanism of action of TMZ has been experimentally well established and is related to the inhibition of the enzyme long-chain 3-ketoacyl coenzyme A thiolase (LC 3-KAT), which is a crucial enzyme in the beta-oxidation pathway. TMZ is also effective in protecting cells from oxygen free radical-induced damage. This antioxidant effect of TMZ was first documented by Maridonneau-Parini and Harpey [60], who demonstrated in human red blood cells that TMZ significantly reduced the loss of intracellular K^+ and the membrane content of peroxidated lipids, as measured by MDA concentrations, induced by oxygen free radicals. Additional studies confirmed these initial results in various animal models. Guarnieri and Muscari [61] showed that TMZ decreased lipid peroxidation in monocrotaline-induced hypertrophy of the rat heart. Abadie et al. [62] studied isolated rat hearts subjected to electrolysis as a source of oxygen free radicals. An abrupt reduction in heart function was observed at the end of electrolysis. The addition of TMZ to the perfusate significantly counteracted the deleterious effects of electrolysis on haemodynamic performance, so that coronary flow, heart rate and isovolumetric left ventricular pressure were significantly improved.

Several authors have investigated the effects of TMZ on glucose utilization in rats and dogs undergoing prolonged ischaemia [63]. They demonstrated a shift of cellular metabolism to preferential glucose utilization by the oxidative pathway, resulting from decreasing fatty acid oxidation in ischaemia, and suggested that this goal could be achieved either by inhibiting beta-oxidation or by blocking CPT. In the study of Kantor et al. [64] TMZ reduced the rate of FFA oxidation, with a concomitant 210% increase in glucose oxidation rates during low-flow ischaemia. Their data also suggested that the likely route by which this was achieved was through the inhibition of the enzyme LC 3-KAT, which is a crucial enzyme in the beta-oxidation pathway. Other authors, however, did not demonstrate any significant inhibitory effects of TMZ on LC 3-KAT or inhibition of other enzymes of beta-oxidation at doses exceeding those which have previously been found to be clinically effective for angina.

Several clinical trials have demonstrated the potential benefits of TMZ in ischaemic heart disease. TRIMPOL II, a large, randomised, controlled trial, enrolled 426 patients with stable angina who were randomised to either TMZ 20 mg three times a day or placebo in addition to metoprolol [55]. This study demonstrated an improvement in time to ST segment depression on exercise tolerance, total exercise workload, mean nitrate consumption and angina frequency in patients randomised to receive TMZ.

In stable effort angina, TMZ improves exercise tolerance and elevates ischaemic threshold as much as beta-blockers or calcium antagonists [66, 67]. When given in combination with beta-blockers, TMZ has a greater anti-ischaemic effect than nitrates and calcium antagonists [68].

Six months of therapy with a modified-release (MR) formulation of TMZ dosed twice daily has been evaluated in patients with stable angina pectoris [69]. Patients in this multinational, randomized, double-blind, placebo-controlled study received atenolol 50 mg per day and MR TMZ 35 mg or placebo for 6 months. Primary efficacy was based on change in time to 1-mm ST-segment depression. Time to 1-mm ST-segment depression was increased significantly with TMZ compared with placebo. Rates of adverse events were similar and no differences in corrected QT intervals were observed between treatment groups.

A meta-analysis of 12 double-blind, randomized, controlled clinical trials of TMZ in the treatment of stable angina was published in 2003 [70]. This analysis of studies conducted from 1986 to 2001 included patients who were treated with TMZ for at least 2 weeks and included controls with placebo or conventional anti-anginal therapy. Trimetazidine was associated with significant reductions in the number of weekly angina attacks, improved time to 1-mm segment depression, and total work at peak exercise. Tolerability of TMZ was mentioned in only 8 of these 12 studies, and was not thoroughly evaluated in most of these trials, mainly because of the excellent tolerability of this drug. Overall, this metaanalysis showed that TMZ was an effective anti-anginal agent when used alone or in combination with traditional haemodynamic agents.

Our group has recently shown that in patients with diabetes and chronic stable angina, the addition of TMZ to standard medical therapy reduces the number of episodes of ST-segment depression, the episodes of silent ischaemia, and the total ischaemic burden [71].

In addition to the anti-ischaemic effect, partial inhibition of FFA oxidation may represent an alternative approach to the treatment of patients with diabetes and heart failure.

Trimetazidine seems to facilitates the recovery of hibernating myocardium. We and others have recently demonstrated that the adjunct of TMZ to standard therapy improves left ventricular systolic and diastolic function of chronically dysfunctional myocardium in patients with type 2 diabetes, CAD and reduced LV function [72, 73].

Ranolazine

Another potential drug in the metabolic management of chronic angina is ranolazine, which reduces the late sodium current, decreasing sodium entry into ischaemic myocardial cells. This drug was initially suggested to block beta-oxidation, while more recently there has been a shift in the proposed mechanism of action for this drug. As a consequence, ranolazine is now proposed to reduce calcium uptake indirectly via the sodium/calcium exchanger and to preserve ionic homeostasis and reverse ischaemia-induced contractile dysfunction [74].

The anti-ischaemic effect of ranolazine is very mild compared to other metabolic agents. Since January 2006, extended-release ranolazine has been approved in the US for use as an add-on therapy in patients with chronic angina. The drug is not approved in Europe.

The MARISA study [75], the first trial of monotherapy with SR ranolazine in patients with chronic angina, assessed the efficacy and tolerability of 3 doses (500, 1000 and 1500 mg) of ranolazine compared with placebo in treadmill exercise performance. All strengths of ranolazine were associated with significant albeit small improvement in total exercise duration, time to angina, and time to 1-mm ST segment depression at both trough and peak time points compared with placebo. Adverse events on ranolazine appeared to be dose related and included dizziness, nausea, asthenia, constipation and prolongation of the QT interval.

The efficacy and tolerability of SR ranolazine in combination with beta-blockers or calcium channel blockers have been investigated in a double-blind,

3-group, parallel trial, the Combination Assessment of Ranolazine In Stable Angina (CARISA) study [76]. Compared with placebo, both doses of SR ranolazine demonstrated an increase in treadmill exercise duration at both trough and peak, an effect that was sustained throughout 12 weeks of therapy.

Both the MARISA and CARISA clinical trials suggest that ranolazine may have some anti-anginal effect. However, its long-term safety, particularly in relation to QT prolongation, remains to be established.

In the more recent ERICA trial [77] that enrolled 565 patients with angina while in treatment with amlodipine, ranolazine reduced frequency of angina compared with placebo.

Until now there are no studies with ranolazine that evaluate the benefit in the subgroup of patients with diabetes.

Preliminary safety concerns observed in clinical trials include dose-related QT prolongation and clinically significant drug interactions.

In conclusions patients with diabetes have impaired myocardial handling of glucose with reduced energy production that is reversed, at least in part, by drugs that improve glucose sensitivity and interfere with beta-oxidation. Up until now the only sound clinical data with metabolic agents in patients with coronary artery disease and diabetes have been obtained with trimetazidine, which should therefore be considered the metabolic drug of choice for these patients.

References

1. Bartnik M, Ryden L, Ferrari R, et al. The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe. Eur Heart J 2004; 25: 1880-90.
2. Langer A, Freeman MR, Josse RG, Steiner G, Armstrong PW. Detection of silent myocardial ischemia in diabetes mellitus. Am J Cardiol 1991; 67: 1073-8.
3. Zarich S, Waxman S, Freeman RT, Mittleman M, Hegarty P, Nesto RW. Effect of autonomic nervous system dysfunction on the circadian pattern of myocardial ischemia in diabetes mellitus. J Am Coll Cardiol 1994; 24: 956-62.
4. Ruderman NB, Haudenschild C. Diabetes as an atherogenic factor. Prog Cardiovasc Dis 1984; 26: 373-412.
5. Haffner SM. Coronary heart disease in patients with diabetes. N Engl J Med 2006; 342: 1040-2.
6. Miettinen H Lehto S, Salomaa V, et al. Impact of diabetes on mortality after the first myocardial infarction. The FINMONICA Myocardial Infarction Register Study Group. Diabetes Care 1998; 21: 69-75.
7. Feener EP, King GL. Vascular dysfunction in diabetes mellitus. Lancet 1997; 350 (Suppl 1): S9-13.
8. Barazzoni R, Kiwanuka E, Zanetti M, Cristini M, Vettore M, Tessari P. Insulin acutely increases fibrinogen production in individuals with type 2 diabetes but not in individuals without diabetes. Diabetes 2003; 52: 1851-6.
9. Memon RA, Saeed SA, Jabbar A, et al. Altered platelet activating factor metabolism in insulin dependent diabetes mellitus. J Pak Med Assoc 1995; 45: 122-5.
10. Haffner SM. Management of dyslipidemia in adults with diabetes. Diabetes Care 1998; 21: 160-78.
11. Ewing DJ, Campbell IW, Clarke BF. The natural history of diabetic autonomic neuropathy. Q J Med 1980; 49: 95-108.
12. Boudina S, Abel ED. Diabetic cardiomyopathy revisited. Circulation 2007; 115: 3213-23.
13. Jorgensen RG, Russo L, Mattioli, Moore WV. Early detection of vascular dysfunction in type I diabetes. Diabetes 1988; 37: 292-6.
14. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993; 329: 977-86.
15. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 52: 837-53.
16. Pan WH, Cedres LB, Liu K, et al. Relationship of clinical diabetes and asymptomatic hyperglycemia to risk of coronary heart disease mortality in men and women. Am J Epidemiol 1986; 123: 504-16.
17. Butler WJ, Ostrander LD Jr, Carman WJ, Lamphiear DE. Mortality from coronary heart disease in the Tecumseh study. Long-term effect of diabetes mellitus, glucose tolerance and other risk factors. Am J Epidemiol 1985; 121: 541-7.
18. Eschwege E, Richard JL, Thibult N, et al. Coronary heart disease mortality in relation with diabetes, blood glucose and plasma insulin levels. The Paris Prospective Study, ten years later. Horm Metal Res Suppl 1985; 15: 41-6.
19. DECODE Study Group; European Diabetes Epidemiology Group. Age, body mass index and glucose tolerance in 11 European population-based surveys. Diabet Med 2002; 19: 558-65.
20. Giugliano D, Ceriello A, Paolisso G. Oxidative stress and diabetic vascular complications. Diabetes Care 1996; 19: 257-67.
21. King GL, Kunisaki M, Nishio Y, Inoguchi T, Shiba T, Xia P. Biochemical and molecular mechanisms in the development of diabetic vascular complications. Diabetes 1996; 45 (Suppl 3): S105-8.
22. Zeng G, Nystrom FH, Ravichandran LV, et al. Roles for insulin receptor, PI3-kinase, and Akt in insulin-signalling pathways related to production of nitric oxide in human vascular endothelial cells. Circulation 2000; 101: 1539-45.
23. Jiang ZY, Lin YW, Clemont A, et al. Characterization of selective resistance to insulin signalling in the vasculature of obese Zucker (fa/fa) rats. J Clin Invest 1999; 104: 447-57.
24. Stanley WC, Lopaschuk GD, Hall JL, McCormack JG. Regulation of myocardial carbohydrate metabolism under normal and ischaemic conditions. Potential for pharmacological interventions. Cardiovasc Res 1997; 33: 243-57.
25. Gertz EW, Wisneski JA, Stanley WC, Neese RA. Myocardial substrate utilization during exercise in humans. Dual carbon-labeled carbohydrate isotope experiments. J Clin Invest 1988; 82: 2017-25.
26. Liedtke AJ. Alterations of carbohydrate and lipid metabolism in the acutely ischemic heart. Prog Cardiovasc Dis 1981; 23: 321-36.
27. McNulty PH, Jagasia D, Cline GW, et al. Persistent changes in myocardial glucose metabolism in vivo during reperfusion of a limited-duration coronary occlusion. Circulation 2000; 101: 917-22.
28. Tamm C, Benzi R, Papageorgiou I, Tardy I, Lerch R. Substrate competition in postischemic myocardium. Effect of substrate availability during reperfusion on metabolic and contractile recovery in isolated rat hearts. Circ Res 1994; 75: 1103-12.

29. Stanley WC. Cardiac energetics during ischaemia and the rationale for metabolic interventions. Coron Artery Dis 2001; 12 (Suppl. 1): S3-7.
30. Taegtmeyer H, Roberts AF, Raine AE. Energy metabolism in reperfused heart muscle: metabolic correlates to return of function. J Am Coll Cardiol 1985; 6: 864-70.
31. Depre C, Vanoverschelde JL, Taegtmeyer H. Glucose for the heart. Circulation 1999; 99: 578-88.
32. Lopaschuk GD, Wambolt RB, Barr RL. An imbalance between glycolysis and glucose oxidation is a possible explanation for the detrimental effects of high levels of fatty acids during aerobic reperfusion of ischemic hearts. J Pharmacol Exp Ther 1993; 264: 135-44.
33. Heusch G. Hibernating myocardium. Physiol Rev 1998; 78: 1055-85.
34. Murnaghan MF. Effect of fatty acids on the ventricular arrhythmia threshold in the isolated heart of the rabbit. Br J Pharmacol 1981; 73: 909-15.
35. Stanley WC, Lopaschuk GD, McCormack JG. Regulation of energy substrate metabolism in the diabetic heart. Cardiovasc Res 1997; 34: 25-33.
36. Ahmed SS, Jaferi GA, Narang RM, Regan TJ. Preclinical abnormality of left ventricular function in diabetes mellitus. Am Heart J 1975; 89: 153-8.
37. Abel ED. Myocardial insulin resistance and cardiac complications of diabetes. Curr Drug Targets Immune Endocr Metabol Disord 2005; 5: 219-26.
38. Regan TJ, Lyons MM, Ahmed SS, et al. Evidence for cardiomyopathy in familial diabetes mellitus. J Clin Invest 1977; 60: 884-99.
39. Zoneraich S, Silverman G, Zoneraich O. Primary myocardial disease, diabetes mellitus, and small vessel disease. Am Heart J 1980; 100: 754-5.
40. Farah AE, Alousi AA. The actions of insulin on cardiac contractility. Life Sci 1981; 29: 975-1000.
41. Rodrigues B, Cam MC, McNeill JH. Metabolic disturbances in diabetic cardiomyopathy. Mol Cell Biochem 1998; 180: 53-7.
42. Osorio JC, Stanley WC, Linke A, et al. Impaired myocardial fatty acid oxidation and reduced protein expression of retinoid X receptoralpha in pacing-induced heart failure. Circulation 2002; 106: 606-12.
43. Stanley WC, Lopaschuk GD, McCormack JG. Regulation of energy substrate metabolism in the diabetic heart. Cardiovasc Res 1997; 34: 25-33.
44. Hall JL, Lopaschuk GD, Barr A, Bringas J, Pizzurro RD, Stanley WC. Increased cardiac fatty acid uptake with dobutamine infusion in swine is accompanied by a decrease in malonyl CoA levels. Cardiovasc Res 1996; 32: 879-85.
45. Nicholl TA, Lopaschuk GD, McNeill JH. Effects of free fatty acids and dichloroacetate on isolated working diabetic rat heart. Am J Physiol 1991; 261: H1053-9.
46. Stettler C, Allemann S, Juni P, et al. Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: Meta-analysis of randomized trials. Am Heart J 2006; 152: 27-38.
47. Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352: 854-65.
48. Corpus RA, George PB, House JA, et al. Optimal glycemic control is associated with a lower rate of target vessel revascularization in treated type II diabetic patients undergoing elective percutaneous coronary intervention. J Am Coll Cardiol 2004; 43: 8-14.
49. Rydén L, Standl E, Bartnik M, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur Heart J 2007; 28: 88-136.
50. Rackley CE, Russell RO, Rogers WJ, Mantle JA, McDaniel HG, Papapietro SE. Clinical experience with glucose-insulin-potassium therapy in acute myocardial infarction. Am Heart J 1981; 102: 1038-49.
51. Malmberg K, Rydén L, Hamsten A, Herlitz J, Waldenström A, Wedel H. Effects of insulin treatment on cause-specific one-year mortality and morbidity in diabetic patients with acute myocardial infarction. DIGAMI Study Group. Diabetes Insulin-Glucose in Acute Myocardial Infarction. Eur Heart J 1996; 17: 1337-44.
52. Malmberg K, Ryden L, Birkeland K, et al. DIGAMI2 investigators. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. Eur Heart J 2005; 26: 650-61.
53. Fath-Ordoubadi F, Beatt KJ. Glucose-insulin-potassium therapy for treatment of acute myocardial infarction: an overview of randomized placebo-controlled trials. Circulation 1997; 96: 1152-6.
54. Horowitz JD, Mashford ML. Perhexiline maleate in the treatment of severe angina pectoris. Med J Aust 1979; 1: 485-8.
55. White HD, Lowe JB. Antianginal efficacy of perhexiline maleate in patients refractory to beta-adrenoreceptor blockade. Int J Cardiol 1983; 3: 145-55.
56. Jeffrey FM, Alvarez L, Diczku V, Sherry AD, Malloy CR. Direct evidence that perhexiline modifies myocardial substrate utilization from fatty acids to lactate. J Cardiovasc Pharmacol 1995; 25: 469-72.
57. Roberts RK, Cohn D, Petroff V, Seneviratne B. Liver disease induced by perhexiline maleate. Med J Aust 1981; 2: 553-4.
58. Bouche P, Bousser MG, Peytour MA, Cathala HP. Pexiline maleate and peripheral neuropathy. Neurology 1979; 29: 739.
59. Morgan MY, Reshef R, Shah RR, Oates NS, Smith RL, Sherlock S. Impaired oxidation of debrisoquine in patients with perhexiline liver injury. Gut 1984; 25: 1057-64.
60. Maridonneau-Parini I, Harpey C. Effects of trimetazidine on membrane damage induced by oxygen free radicals in human red cells. Br J Clin Pharmcol 1985; 20: 148-51.
61. Guarnieri C, Muscari C. Effect of trimetazidine on mitochondrial function and oxidative damage during reperfusion of ischemic hypertrophied rat myocardium. Pharmacology 1993; 46: 324-31.
62. Abadie C, Ben Baouali A, Nadeau R, Rochette L. Myocardial dysfunction induced by electrolysis as a source of oxygen free radicals: Effect of trimetazidine and serum albumin. J Mol Cell Cardiol 1993; 25 (Suppl. 4): S40.
63. Grynberg A. Regulation of cardiac metabolism at the membrane lipid level. J Mol Cell Cardiol 1997; 29: A33.
64. Kantor PF, Lucien A, Kozak R, Lopaschuk GD. 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 2000; 86: 580-8.
65. 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 2001; 22: 2267-74.
66. Chazov EI, Lepakchin VK, Zharova EA, et al. Trimetazidine in Angina Combination Therapy – the TACT study: trimetazidine versus conventional treatment in patients with stable angina pectoris in a randomized, placebo-controlled, multicenter study. Am J Ther 2005; 12: 35-42.

67. O'Meara E, McMurray JJV. Myocardial metabolic manipulation: a new therapeutic approach in heart failure? Heart 2005; 91: 131-2.
68. Fox K, Garcia MA, Ardissina D, et al. Guidelines on the management of stable angina pectoris: executive summary: the Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J 2006; 27: 1341-81.
69. Sellier P, Broustet JP. Assessment of anti-ischemic and antianginal effect at trough plasma concentration and safety of trimetazidine MR 35 mg in patients with stable angina pectoris: a multicenter, double-blind, placebo-controlledstudy. Am J Cardiovasc Drugs 2003; 3: 361-9.
70. Marzilli M, Klein WW. Efficacy and tolerability of trimetazidine in stable angina: a meta-analysis of randomized, double-blind, controlled trials. Coron Artery Dis 2003; 14: 171-9.
71. Marazzi G, Wajngarten M, Vitale C, et al. Effect of free fatty acid inhibition on silent and symptomatic myocardial ischemia in diabetic patients with coronary artery disease. Int J Cardiol 2007; 120: 79-84.
72. Vitale C, Wajngaten M, Sposato B, et al. Trimetazidine improves left ventricular function and quality of life in elderly patients with coronary artery disease. Eur Heart J 2004; 25: 1814-21.
73. Ciavolella M, Greco C, Tavolaro R, et al. Acute oral trimetazidine administration increases resting technetium 99m sestamibi uptake in hibernating myocardium. J Nucl Cardiol 1998; 5: 128-33.
74. Belardinelli L, Shryock JC, Fraser H. The mechanism of ranolazine action to reduce ischemia-induced diastolic dysfunction. Eur Heart J 2006; 8 (Suppl A): A10-6.
75. Chaitman BR, Skettino SL, Parker JO, et al. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. J Am Coll Cardiol 2004; 43: 1375-82.
76. Chaitman BR, Pepine CJ, Parker JO, et al. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. JAMA 2004; 291: 309-16.
77. Stone PH, Gratsiansky NA, Blokhin A, Huang IZ, Meng L; ERICA Investigators. Antianginal efficacy of ranolazine when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine in Chronic Angina) trial. J Am Coll Cardiol 2006; 48: 566-75.