Improving Survival for Patients with Type 2 Diabetes and Coronary Artery Disease

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Type 2 diabetes is a well-known independent risk factor for coronary artery disease, and its presence adds substantially to any risk conferred by other factors. In the absence of known coronary heart disease, patients with type 2 diabetes have a risk of future cardiovascular disease equal to a nondiabetic patient with one prior myocardial infarction. Type 2 diabetes also modifies the consequences of established coronary heart disease or congestive heart failure in numerous respects. For example, once a patient has sustained a myocardial infarction, the risk of complications and death are about twice as high among patients with diabetes compared to a nondiabetic population. The risk of late complications after angioplasty is higher among patients with diabetes, as is the risk of graft closure among patients with diabetes after bypass surgery. Left heart failure is at least twice as common in diabetic patients compared with the age matched control population. Interestingly, the prevalence of congestive heart failure complicating a myocardial infarction is greater among diabetic patients at equal ejection fractions, evidence that diabetics are more likely to experience diastolic and systolic dysfunction. Type 2 diabetes is associated with premature development of coronary heart disease and worse outcomes after therapy.

Interventions to improve survival for patients with coronary heart disease have been exhaustively evaluated in well-designed trials over the last 20 years. Their value for a large subset of these patients, those with type 2 diabetes, is not well understood because diabetics are underrepresented in many of the important trials. Scattered evidence suggests that some interventions actually confer a greater survival benefit effect among patients with type 2 diabetes, and that other therapies may be less effective compared to outcomes in nondiabetic patients. This uncertainty is regrettable because three of five patients with type 2 diabetes mellitus die of coronary artery disease. Considering the prevalence of type 2 diabetes and the extraordinary morbidity and mortality added by this disease, it is surprising that only a small handful of prospective randomized clinical trials have addressed two questions: Are standard therapies for coronary disease as effective in type 2 diabetes compared to nondiabetic patients? What are the effects of hypoglycemic therapy on the progression of coronary disease?

Selected trials will be reviewed with an emphasis on insights for managing patients with both type 2 diabetes and coronary heart disease. Since the first manifestations of coronary artery disease may be evident within only a few years after the diagnosis of type 2 diabetes (unlike the situation with type 1 diabetes), these comments may be relevant soon after diagnosis. The focus will be on drug and revascularization therapies. Although results from patients with type 1 compared to type 2 diabetes are often not reported separately in subset analyses of larger trials, type 2 diabetes usually predominates. Diet, exercise, estrogen replacement therapy, weight control, and smoking cessation all represent important opportunities for reducing cardiovascular risk, but they are beyond the scope of this summary.

MECHANISMS OF ACCELERATED CORONARY ARTERY DISEASE

Type 2 diabetes mellitus is a complex disorder that is due to a combination of insensitivity to the effects of insulin plus relatively impaired output of insulin by the pancreas. Intrauterine growth retardation, genetic predisposition to obesity and genetic predisposition to insulin resistance have all been postulated as important factors. Once a western lifestyle is imposed on this background, the risk of type 2 diabetes is high. A further confounding factor is that type 2 diabetes is associated with other genetically determined risk factors such as hypertension and dyslipidemia (77, 78). In its later manifestations, type 2 diabetes is a multiorgan disorder with diverse complications. Hence, the factors responsible for the adverse outcomes among patients with coronary artery disease are difficult to disentangle, but have been attributed to two factors: 1) the severity, distribution and progression of coronary artery disease increases risks and reduces the efficacy of therapy, and 2) altered perception of ischemia. The metabolic environment that causes the abnormal progression of coronary disease is thought to be a complex interaction among hyperglycemia, dyslipidemia, and clustering of other genetically and environmentally determined risk factors.

Hyperinsulinemia and hyperglycemia

Insulin resistance and hyperinsulinemia are the characteristic defects of type 2 diabetes that have been reviewed extensively (42). Insulin resistance simply means that some organs do not respond normally to the effects of insulin. Skeletal muscle may be particularly important since it resists the effects of insulin on stimulation of glucose uptake. Resistance by adipose tissue may also play a key role since it influences lipoprotein metabolism (described below). However, other cells may remain sensitive to some effects of insulin. It stimulates arterial smooth muscle proliferation and deposition of connective tissue in arteries, and it has complex effects on the coagulation system. Because of these effects, hyperinsulinemia has been suggested to be a key factor in premature coronary artery disease. Hyperinsulinemia precedes the diagnosis of type 2 diabetes, and it clusters with other cardiovascular risk factors such as hypertension. However, in spite of the theoretical support for an adverse effect of insulin on progression of coronary disease, epidemiological and cross-sectional clinical studies are ambiguous. In some studies, hyperinsulinemia is associated with coronary artery disease. Although this relation could indicate an atherogenic potential of insulin, elevated insulin levels may be a consequence of an underlying factor, insulin resistance, that is itself associated with coronary disease. The intrinsic disease process is also more likely to be severe among patients with insulin-treated diabetes (50, 88). There is also direct evidence against a clinically significant atherogenic effect of insulin in patients with diabetes. In the United Kingdom Prospective Diabetes Study involving relatively healthy newly diagnosed type 2 diabetics, fasting insulin was not correlated with either myocardial infarction or new onset angina (4). Surprisingly, hyperinsulinemia may be a risk factor for CAD only in patients without diabetes.

Table 1. Definition of atherogenic dyslipidemia (26).

- Increased triglyceride levels, usually 150 - 250 mg/dL, occasionally higher
- Depressed high-density lipoprotein (HDL)-levels, less than 40 mg/dL
- Mildly increased low-density lipoprotein (LDL) levels, between 130 and 159 mg/dL
- Increased levels of small dense LDL particles

Hyperglycemia, by contrast, strongly correlates with cardiovascular morbidity and mortality (43). Even in nondiabetics, hyperglycemia confers an increased risk of death from all causes and from coronary heart disease in men. Based on this and other observations, it has been suggested that "the clock for coronary heart disease starts ticking before the onset of clinical diabetes" (7, 32). The mechanism by which hyperglycemia could promote large vessel complications is not known but is likely linked to generation of advanced glycation end products. These glycated products may inhibit the effects of nitrous oxide and damage endothelial cells. Glycated end products in the arterial vessel wall may reduce vascular compliance and increase diastolic shear forces on the endothelium.

In sum, both hyperinsulinemia and hyperglycemia could play a role in promoting coronary artery disease (18). Clinical evidence supports a close correlation of coronary artery disease with sustained hyperglycemia (33), but the independent significance of hyperinsulinemia is less convincing.

Atherogenic dyslipidemia

Patients with type 2 diabetes with reasonable control of blood glucose generally have LDL cholesterol similar to the nondiabetic population. Since dramatic elevation of LDL is not common among type 2 diabetes, therapy may focus solely on the hyperglycemia. However, since excellent control of blood glucose does not "normalize" the risk of cardiovascular complications, there are other factors which are not being corrected. Modestly increased triglyceride-rich lipoproteins (mainly VLDL) and decreased HDL particles, termed "atherogenic dyslipidemia" are more common features of type 2 diabetes and may both play a role in accelerated coronary disease (34).

The interaction of type 2 diabetes with lipoprotein metabolism has been extensively investigated. As noted above, insulin resistance impairs the normal inhibition of fatty acid release from adipose tissue, that is, fatty acids are released from adipose tissue and delivered to the liver at an abnormally high rate. A normal function of insulin is to balance the generation of triglycerides from the liver with generation from the gastrointestinal tract after a meal. With sustained delivery of free fatty acids from the periphery in type 2 diabetes, the liver may be forced to inappropriately produce triglycerides which favors hypertriglyceridemia. Further complicating the picture is the influence of type 2 diabetes on catabolism of triglyceride rich lipoproteins. Lipoprotein lipase hydrolyzes triglycerides to free fatty acids for oxidation in tissues like the heart and skeletal muscle. Lipoprotein lipase is generally reduced somewhat in type 2 diabetes. Thus, the hypertriglyceridemia of type 2 diabetes is multifactorial and relates to both overproduction and underutilization of triglycerides.

The other characteristic feature of diabetic dyslipidemia, depressed HDL, may be related to the hypertriglyceridemia and in particular the delayed metabolism of triglyceride rich lipoproteins. This prolonged residence time in the blood and slow metabolism of triglyceride rich lipoproteins reduces the availability of surface remnants which must be incorporated into the HDL. Further, triglycerides are thought to be exchanged with the HDL core which increases their catabolic rate, also reducing HDL levels.

The excess risk of coronary events in patients with type 2 diabetes is due at least in part to this dyslipidemia. Hypertriglyceridemia and depressed HDLs probably play significant and independent roles. The importance of recently emphasized small dense LDLs in atherogenesis in these patients is less clear (67).

Atherothrombotic state

The potential effects of type 2 diabetes on the coagulation and fibrinolytic systems are complex. The constellation of high triglycerides plus vascular disease plus abnormalities of the coagulation cascade has been described as the atherothrombotic state. There is evidence that hypertriglyceridemia may be weakly associated (13) with a decreased fibrinolytic capacity due to elevated of plasminogen activator inhibitor (PAI-1). The concentration of PAI-1 also is increased by hyperinsulinemia. Other factors being equal, these effects would decrease fibrinolysis. Endothelial dysfunction may further increase the risk of thrombosis and platelet adhesion.

Impaired arteriogenesis

Angiogenesis is defined as the sprouting of new capillaries (73). Arteriogenesis is defined as the structural enlargement, remodeling and growth of arterioles into functioning collateral arteries (73). One histological difference, of course, is that capillaries lack smooth muscle cells and are therefore likely to rupture. The physiological difference is that coronary flow can be substantial through collateral arteries. More recently it has also become apparent that the physiological stimulus for angiogenesis, hypoxia, plays little if any role in arteriogenesis. Since diabetes stimulates angiogenesis in the retina, it might be anticipated that collateral arteries are also more prominent in diabetics. In a recent angiographic study (1) patients with diabetes were less likely to demonstrate coronary collateral arteries in spite of having somewhat more extensive coronary artery disease. In spite

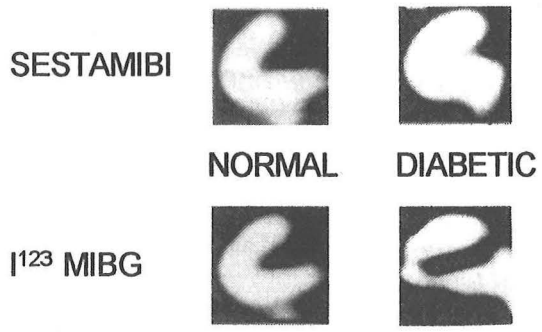

Figure 1. Dual imaging with sestamibi (perfusion) and MIBG in a normal control and a patient with diabetes. From reference 46.

of numerous limitations in this study (retrospective, uncontrolled, nonrandomized, coronary artery evaluation by visual inspection) it nevertheless suggests another reason why patients with diabetes may not tolerate coronary artery disease.

Autonomic dysfunction and silent ischemia

Silent ischemia, defined as ST depression without obvious symptoms, is more common among people with diabetes during normal activities or on a treadmill test (87). Similarly, silent myocardial infarction, defined as new Q waves on surveillance electrocardiograms without obvious symptoms, are more common among patients with diabetes mellitus (57). The inability of patients with diabetes mellitus to perceive or communicate symptoms of ischemia may contribute to the increased risk of cardiac complications, particularly after PTCA or in the period after an MI.

A distinct but conceivably related abnormality among patients with diabetes mellitus is the apparently attenuated parasympathetic innervation. This results in an increased heart rate, abnormal circadian variation in heart rate, and may cause QT prolongation which may increase the risk of arrhythmic death (21, 85). This suggestion may have direct clinical significance in two respects. First, optimal glycemic control may reduce the development of the autonomic neuropathy. Second, ß-blockers increase heart rate variability after MI, (72), ß-blockers may be particularly indicated among diabetic patients with atypical or absent symptoms of ischemia.

The cardiac autonomic dysfunction of type 2 diabetes has been assessed recently using ^{123}I - labeled metaiodobenzylguanidine (MIBG, see Figure 2). It is a norepinephrine analogue that is actively transported into sympathetic nerve terminals. MIBG imaging is considered to reflect cardiac sympathetic innervation. Although MIBG uptake was not always uniform in the normal controls, it was more inhomogeneous amog patients with diabetes and uptake of MIBG was reduced (46).

HYPERGLYCEMIA

Traditionally, therapy for patients with type 2 diabetes focuses on normalizing glucose levels as monitored by the hemoglobin A_{1c}. For patients with coronary disease, the wisdom of this approach depends on the answer to two questions: 1) Will control of hyperglycemia reduce the risk of future coronary events? and 2) Does the therapy itself make any difference? This topic is far beyond the scope of this review, but one basic controversy revolves around the value of controlling blood glucose by increasing blood insulin. Since hyperinsulinemia is thought to be undesirable, it is theoretically most attractive to improve insulin sensitivity through weight loss and exercise or through pharmacologic therapy with either a thiazolidinedione or metformin which will reduce both insulin and glucose levels. Two other agents, sulfonylureas and insulin, lower glucose by increasing insulin levels. If hyperinsulinemia per se has contributes to the progression of CAD, then these approaches may be undesirable.

Table 2. First events among 1,441 patients with type 1 diabetes randomized to conventional or intensive insulin therapy. From reference 16.

	conventional	intensive
fatal cardiac event	1	1
sudden death	0	1
nonfatal cardiovascular	13	1
Major peripheral event	26	20
TOTAL	**40**	**23**

Sulfonylureas

Sulfonylureas are the most widely used oral hypoglycemic agents. Although they are effective in reducing plasma glucose, for the last 30 years their safety for patients with known or suspected CAD has been in doubt because of results from the University Group Diabetes

Program (82). Patients with diabetes who were treated with tolbutamide experienced a higher cardiovascular mortality rate compared to patients treated with placebo. This study was widely criticized, but, since there were few alternatives for glucose control, their use was continued. More recently (80) there was no increase in cardiovascular events with sulfonylurea therapy.

Sulfonylureas have complex nonpancreatic effects which appear to be closely related to the mechanism of insulin release in the β cell (47, 76). Under normal conditions an increase in blood glucose is thought to increase intracellular [ATP] which in turn inhibits potassium flux through the K_{ATP} channel, increases intracellular potassium and stimulates insulin release. Sulfonylureas close the ATP sensitive potassium channels in pancreatic β cells which enhances insulin secretion. Receptors for sulfonylureas are also present in the myocardium, but normally in cardiomyocytes the K_{ATP} channels are closed because of high levels of intracellular ATP. Little effect of sulfonylureas would be anticipated under normal conditions, but during ischemia a number of factors (intracellular acidosis, ATP depletion and accumulation of ADP) may allow opening of the K_{ATP} channels. Under these conditions sulfonylureas could conceivably influence the "normal" response to ischemia. Sulfonylureas increase the size of experimental myocardial infarction in animals, and the potassium ion channels may play also a role in ischemic preconditioning. Interestingly, sulfonylureas reduced the sensitivity of the surface ECG to ischemia. This property, if clinically relevant, could decrease the sensitivity of the ECG to ischemia, possible in patients with atypical chest discomfort when an accurate ECG might be most important.

In addition to the UGDP study, there is other evidence that sulfonylureas have adverse effects in patients with coronary disease. Sulfonylureas are weak vasoconstrictors and have been reported to worsen outcomes after both elective (64) and urgent (24) coronary angioplasty. Thus, in spite of their glucose-lowering effects on insulin secretion, nonpancreatic activity may counterbalance these benefits. Some of the newer members of this drug class have reduced nonpancreatic activity and theoretically may have fewer adverse effects on the cardiovascular system.

Against this background, however, a recent analysis of about 25,000 patients on sulfonylureas and 19,000 patients on insulin from the Cooperative Cardiovascular Project found no adverse effects of sulfonylureas on cardiovascular mortality (35). Sulfonylureas were not associated with increased rates of complications or death after an MI in this older population. In sum, in spite of the very widespread use of sulfonylureas, their safety for patients with coronary artery disease is unclear.

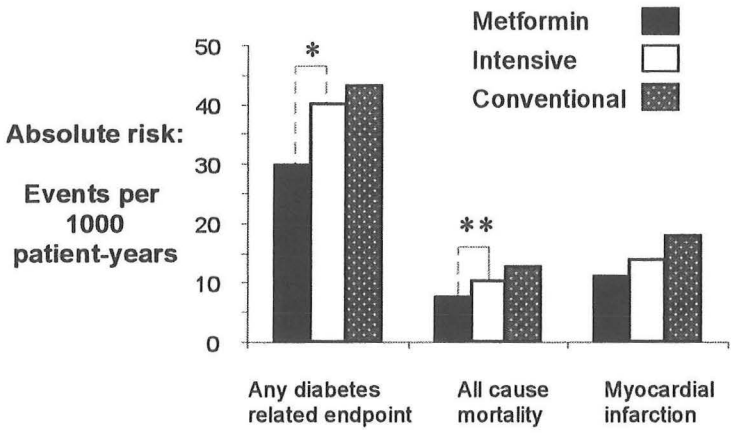

Figure 2. Clinical endpoints among patients assigned intensive control with metformin (n=342), intensive control with chlorpropamide, glibenclamide, or insulin (intensive; n=951), or conventional control (n=411). *, $p< 0.01$; **, $p< 0.05$. From the UKPDS.

Insulin

If insulin promotes atherosclerosis then administration of insulin to a patient with high risk for coronary disease is inappropriate. Alternatively, it is plausible that the benefit of tight glucose control outweighs this risk.

Some insight into the potential value of tight glucose control comes from the Diabetes Control and Complications Trial (DCCT). This study was restricted to young patients (13-39 years) with type 1 diabetes but

without known coronary artery disease and without hypertension or hypercholesterolemia (15,16). The key finding, of course, was that intensive treatment reduced the risk of nephropathy, retinopathy and neuropathy, an observation confirmed in other studies (68). The investigators also reported the risk of coronary events, although the trial was not designed to investigate the effect of insulin on coronary disease. In the conventional treatment group (Table 2) there were 40 events and in the intensive group there were 23 events, although the difference was not statistically significant ($p = 0.08$). Patients enrolled in the intensive treatment are had a two fold increase in the risk of severe hypoglycemia. These results are consistent with the notion that tight control reduces the risk of major cardiac events, but at the risk of significant hypoglycemic episodes.

These established benefits of insulin in type 1 diabetes and the trend for reduced complications related to coronary disease cannot be extended from patients in the DCCT to patients with type 2 diabetes since the latter often have vascular disease at the time of presentation and are often much older with associated risk factors such as hypertension and hypercholesterolemia that were excluded in DCCT. Further, the consequences of severe hypoglycemia in an older patient with vascular disease may be more serious than in a young patient without established atherosclerosis.

A small number of randomized trials do have arms that compared intensive or moderately intensive insulin therapy to an alternative. Each of these trials is in some respect unsatisfactory. The UGDP has design flaws that have been extensively reviewed. The DIGAMI, discussed below, only enrolled patients immediately after an MI and may not be relevant to other patients. The UK and Japanese (63) trials enrolled relatively healthy patients, and the VA pilot study was quite small. None of these trials adequately addresses whether insulin therapy in type 2 diabetes accelerates the progression of coronary artery disease, but on the balance (Table 3) a clear adverse effect of insulin has not been demonstrated.

Hyperinsulinemia is probably best considered to be associated with other risk factors. Based on this conclusion and the beneficial effects of insulin after MI (see below), control of hyperglycemia with insulin even in patients with coronary artery disease is a reasonable option.

Table 3. Randomized prospective trials of insulin compared to an alternative therapy among patients with type 2 diabetes: influence on coronary events.

	Design	Result
DIGAMI ref: 52,53	Insulin compared to oral agents	Insulin better
UGDP ref: 82	Insulin compared to sulfonylurea	Insulin better
UKPDS Ref: 81	Insulin compared to sulfonylurea	Insulin equivalent
VA Ref: 2	Tight control with insulin compared to insulin	Tight control with insulin worse*
UKPDS Ref: 81	Insulin compared to metformin	Insulin worse

*marginal statistical significance in a small trial

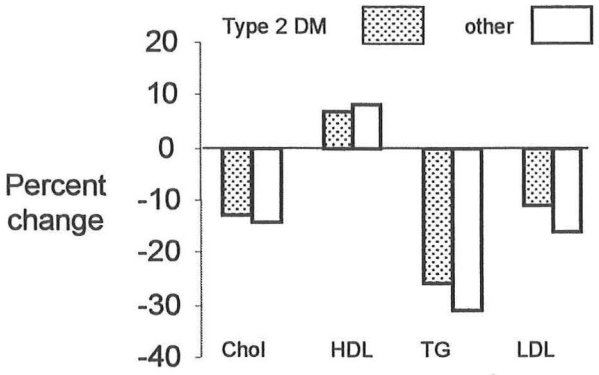

Figure 3. Effects of gemfibrozil on lipids. The response of patients with type 2 diabetes compared to nondiabetic patients is shown. Results redrawn from the Helsinki Heart Trial.

Metformin

Metformin reduces hyperglycemia by enhancing insulin sensitivity and suppressing hepatic glucose output which together result in a decrease in both insulin and glucose levels. It also has the advantage of less weight gain. Since metformin as monotherapy is nearly as effective as a sulfonylurea in decreasing blood glucose, it makes sense to use it in patients with type 2 diabetes. This agent was studied in a prospective trial of patients with type 2 diabetes and obesity (81). Considering all cause mortality, metformin achieved a 36% reduction compared to either insulin or a sulfonylurea. Metformin is a biguanide, like phenformin which is no longer on the market because of a risk of lactic acidosis. The adverse effects of metformin include a very rare lactic acidosis and it is contraindicated among patients with mild renal insufficiency and under conditions of reduced cardiac output. In spite of these concerns, the beneficial effects on both plasma insulin and glucose, the overall safety record, and the demonstrated mortality benefits make it a logical first line agent if adequate control can be achieved. As monotherapy, metformin is unlikely to perform better than a sulfonylurea in terms of glucose control. Combination of two complementary oral agents or combination of metformin (which increases sensitivity to the effects of insulin) with insulin to reduce the insulin dose could be justified. Unfortunately, whether these combinations have an influence on cardiovascular complications is not known.

Troglitazone

Troglitazone, one of the recently introduced thiazolidinediones, improves insulin sensitivity in skeletal muscle and liver. It is nearly as effective as sulfonylureas in reducing glycated hemoglobin (74). The insulin-sensitizing effect has the theoretical advantage of improving a fundamental defect in type 2 diabetes, and therefore it is an attractive long-term agent. Troglitazone also lowers triglycerides and increase HDLs. An asymptomatic hepatocellular injury, usually manifest as an increase in serum transaminases, has been reported in 1-2% of patients. A small number of patients have sustained severe injury (84). Since metformin decreases hepatic glucose production and troglitazone increases insulin sensitivity, it may be attractive to combine these agents because of differing mechanisms of action. The combination of metformin and troglitazone is effective and well-tolerated, but the effects on progression of coronary disease are unknown (30).

DYSLIPIDEMIA

As noted, type 2 diabetes is often associated with an abnormal lipid profile that may be causative in the progression of coronary disease. Aerobic training, a high fiber diet, estrogen replacement therapy where appropriate and weight loss may significantly improve the lipid profile. However, if these measures are unsuccessful, specific pharmacotherapy, integrated into therapy for hyperglycemia, is indicated. Since the association between triglycerides and subsequent coronary events seems to be strong in patients with type 2 diabetes, hypertriglyceridemia deserves particular attention. Subgroup analyses of three large trials have been reported (Table 4).

The benefits of treating dyslipidemia in diabetics has been reported in subset analyses from three larger studies. The Helsinki Heart Study (HHS, ref 41) enrolled 4081 men, of whom 135 had type 2 diabetes at entry. Criteria for diagnosis included diet treated diabetes (93 patients), fasting hyperglycemia (26 patients), or treatment with oral hypglycemics (16 patients). The incidence of coronary events, defined as myocardial infarction or cardiac death, was significantly greater among patients with type 2 diabetes than among nondiabetics over 5 years. Among the patients with type 2 diabetes, the risk of coronary events was 3.4% on gemfibrozil and 10.5% on placebo. This difference was not statistically significant ($p = 0.19$) but the trend for this low-risk population favored gemfibrozil. Within the entire study, the patients who benefited the most were those with low HDL and high triglycerides, that is, among patients with the atherogenic dyslipidemia profile. Although type 2 diabetes may disrupt normal triglyceride and HDL metabolism, a differential effect of gemfibrozil on lipids in patients with diabetes was not detected (Figure 3). High triglycerides may predict beneficial effects from gemfibrozil (56).

Table 4. Subgroup analysis of three trials of lipid-lowering treatment: 5 year risk of coronary events.

STUDY (total pts)	Patients with diabetes	Patient features	Intervention	Events on placebo	Events on therapy
HHS (4,081) ref: 41	135	No known CAD, non-HDL cholesterol > 200 mg/dL	gemfibrozil	10.5	3.4
CARE (4,159) ref: 71	586	Prior MI, average cholesterol was 209 mg/dL	pravastatin	37	29
SSSS (4,444) ref: 66	202	Prior MI or angina, average cholesterol was 262 mg/dL	simvastatin	45	23

The Scandinavian Simvastatin Survival Study (SSSS) enrolled patients with prior MI or angina, and reported on the subset of patients with diabetes. Patients had increased total cholesterol, but triglycerides were less than 220 mg/dL. In that study, the difference between placebo (25% mortality) and simvastatin (14% mortality) was not significant, but the risk of a cardiac event was reduced among patients with type 2 diabetes, with a risk reduction similar to nondiabetic patients.

The Cholesterol and Recurrent Events Trial (CARE) enrolled patients with prior myocardial infarction and average cholesterol levels, 209 mg/dL. Among those with diabetes, the major coronary event rate was reduced from 37% on those treated with placebo to 29% for those on pravastatin, a difference that was statistically significant ($p < 0.05$). Interestingly, the greatest benefit in the overall trial was among patients with triglycerides less than 144 mg/dL.

These trials suggest that treating dyslipidemia among patients with diabetes confers approximately the same benefit, defined as relative risk reduction for coronary events, as similar treatment among patients without diabetes. Other benefits may accrue from cholesterol lowering therapy such as retarding diabetic nephropathy (45). Unfortunately, the absolute event rate is higher for all patients with diabetes, whether or not they receive therapy. Hence, patients with diabetes benefit at least as much as patients without diabetes, but the therapy does not normalize the risk, i.e., bring the risk down to the level of a nondiabetic patient.

A statin is indicated among patients with type 2 diabetes mellitus and hypercholesterolemia with normal or mildly elevated triglycerides. Among patients with low HDL and marked elevation of triglycerides, gemfibrozil should be considered. Combination of fibrates and a statin theoretically offer optimal treatment of the diabetic dyslipidemia, but the effects on coronary events are unknown, and rhabdomyolysis has been reported (65).

Patients with diabetes often have a recently characterized form of LDL which is smaller and denser than normal LDL particles. Since these particles are easily oxidized, antioxidant therapy may prevent coronary artery disease. One trial suggested that vitamin E reduces the risk of infarction, but this was not confirmed in two recent reports.

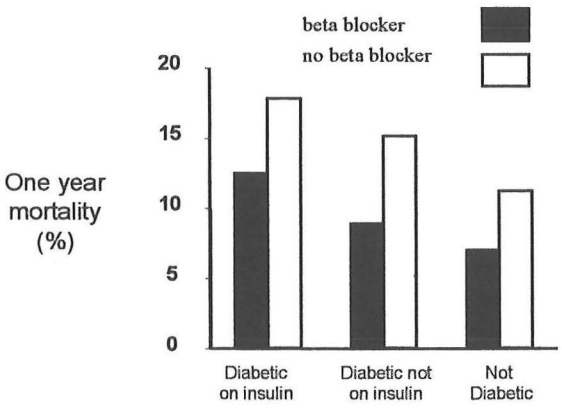

Figure 4. Effect of outpatient beta blocker therapy on one year mortality among elderly patients with diabetes who survived a myocardial infarction. From data in reference 12.

Niacin is effective in improving the profile of atherogenic dyslipidemia. It improves levels of HDL, triglycerides, and small dense LDL. Interestingly it also improves levels of Lp(a) lipoprotein, fibrinogen, and plasminogen activator inhibitor-I. Thus, unlike other agents, it improves some of the hemostatic abnormalities that may contribute to the risk of coronary disease. However, in nondiabetics niacin increases fasting glucose levels but does not increase Hb A_{1C}. Glycemic control may deteriorate among patients with type 2 diabetes on niacin. In general, the concerns of impaired glycemic control plus the symptomatic side effects of niacin seem to outweigh its benefits, and niacin is not widely used for management of dyslipidemia among patients with type 2 diabetes.

ANGINA

Calcium-channel blockers are safe antianginal agents in diabetic patients. In one report (11), they had no effect on mortality among patients with diabetes. The dyslipidemia and glucose control were not affected. Nitrates are effective among patients with diabetes, but some may require higher doses (58).

Table 5. Subgroup analysis of beta blocker trials

STUDY (total pts)	Number of patients with diabetes	Duration of followup (months)	intervention	Cardiac mortality in diabetics	Cardiac mortality in nondiabetics
BHAT (4,163) ref: 39	55	25	propranolol	↓ 35%	↓ 25%
Norwegian (1,884) ref: 28	99	17	timolol	↓ 63%	↓ 34%
Goteberg (1,395) ref: 51	120	3	metoprolol	↓ 58%	↓ 30%

β adrenergic blockers

ß-blockers impair the sensation of hypoglycemia (14) and for this reason have traditionally been avoided in patients with diabetes because they may mask adrenergically - mediated symptoms of hypoglycemia (59). The American Heart Association and American College of Cardiology previously indicated that insulin use is a relative contraindication to use of ß blockers (70). However, hypoglycemia is a rare complication of beta blockers (25, 44), so the relevant question is whether patients with diabetes mellitus actually benefit from ß blockers. The important cardiac indications for ß-blockers with type 2 diabetes are to 1) reduce mortality after myocardial infarction, 2) improve survival for patients with a dilated cardiomyopathy, and 3) treat unstable angina (36, 37).

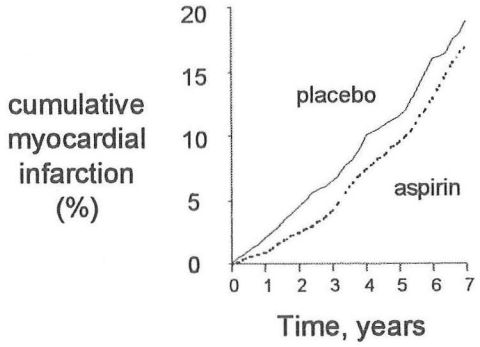

Figure 5. Effect of aspirin on myocardial infarction among patients with diabetes (20).

Although the ideal studies have not been performed to analyze the efficacy of ß-blockers for each of these indications among patients with diabetes, in general, the benefit for patients with diabetes mellitus is at least as great for patients without diabetes. Among a population of patients with type 2 diabetes, those patients treated with ß-blockers have lower mortality than patients with diabetes who are not taking ß-blockers. Perhaps the strongest evidence of benefit comes from a randomized trial of atenolol among patients at risk of cardiac complications during noncardiac surgery. Diabetic patients randomized to atenolol, compared with non-diabetic patients, had no increased risk of death. Diabetic patients randomized to placebo had a four-fold increase in risk (55). Finally, results from subgroup analysis of the large secondary prevention trials also support β blockers (Table 5).

The use of β - blockers to manage hypertension is less attractive because of the availability of ACE inhibitors (see below).

Table 6. Effects of antiplatelet therapy on vascular events. Data from reference 5.

	Number of patients assigned to a treatment group		Number of vascular events (%)	
	antiplatelet	control	antiplatelet	control
Diabetes	2248	2254	18.5	22.3
No diabetes	21136	21197	12.8	18.4

Aspirin

Among patients with diabetes at high risk for vascular disease or with known vascular disease, the Antiplatelet Trialists' Collaboration found a benefit of antiplatelet treatment in people with diabetes. The magnitude of that benefit was similar to the benefit among patients without diabetes. In a specific trial enrolling only diabetics on high dose (650 mg/day) aspirin, the Early Treatment Retinopathy Study found that aspirin reduced cardiac events over 7 years. Furthermore, aspirin did not increase intraocular bleeding among those patients with retinopathy. One caveat was raised by the ISIS-2 trial which found that patients

with diabetes mellitus did not benefit from aspirin at 150 mg / day (31). Since hyperglycemia may reduce the immediate antiplatelet effect of aspirin, perhaps a higher initial dose of aspirin is appropriate among patients with hyperglycemia in the setting of an unstable coronary syndrome. Of course, control of hyperglycemia may also be beneficial.

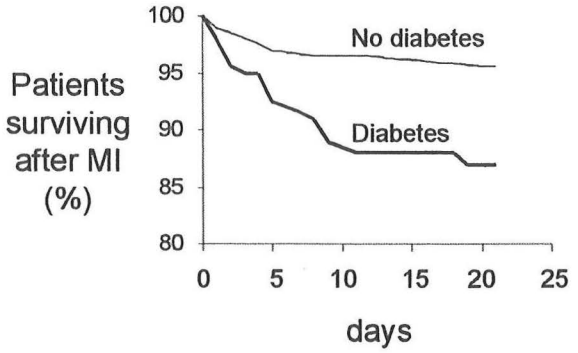

Figure 6. The effects of diabetes on early survival after myocardial infarction. Redrawn from reference 86.

HYPERTENSION

Hypertension is often associated with type 2 diabetes and is often present at the time of diagnosis. Perhaps the most important point to appreciate is that even mild hypertension amplifies the risk of coronary disease and vascular complications among diabetics. Control of blood pressure is associated with preserved renal function, and angiotensin-converting enzyme inhibitiors reduce the rate of progression of nephropathy in both type 1 and type 2 diabetes (48). Presumably, delay in progression of renal disease reduces the risk of cardiovascular complications, but this is not known. It is also likely that ACE inhibitors improve endothelial dysfunction which may be important in patients at high risk for coronary disease (54). In at least one report (19), fatal and nonfatal infarctions were more frequent in type 2 diabetics on nisoldipine compared to enalapril.

Very recently, ramipril was shown to have remarkable beneficial effects among patients at high risk for cardiovascular disease but without heart failure or known left ventricular dysfunction (29). In this study 38% of the participants had diabetes, and the magnitude of the beneficial effects were similar among patients with and without diabetes. The benefit of ramipril was almost certainly not due to its antihypertensive effects which were trivial in this study. It is interesting that ramipril had no effect on the more severe manifestations of either coronary disease or left heart failure such as hospitalization for congestive heart failure, hospitalization for angina, and angina associated with ECG changes. It is not clear if the benefits of ramipril in this relatively healthy population are a class effect, but similar studies underway with other ACE inhibitors should prove helpful.

Table 7. Effects of ramipril on primary and selected secondary endpoints in the HOPE trial. All results are in percent, and all differences in this table (ramipril vs. placebo) where statistically significant (29).

	MI, stroke, CV death	revascularization	New diabetes	All CHF
Ramipril	14	16.0	3.6	11.5
Placebo	17.8	18.3	5.4	9.0

Generally, cardioselective ß-blockers, calcium channel blockers and ACE inhibitors are all suitable for management of hypertension among patients with diabetes, and thiazide diuretics should be avoided. These recent results may indicate that ACE inhibitors are the first line of therapy for hypertension, and raise the question of whether all patients with type 2 diabetes should be on ramipril.

ACUTE MYOCARDIAL INFARCTION

Diabetics with a myocardial infarction are more likely to be older and female compared to a nondiabetic population, and they tend to seek medical attention later in the course of the infarction. Left ventricular function tends to be worse in patients with diabetes, and they have a higher incidence of

multivessel disease. Thus, it is not surprising that prospective trials found that insulin treated diabetics had an early mortality of twice control and noninsulin treated diabetics a mortality of about 1.5 times control (Figure 6). However, analysis of the mechanism of this excess mortality is difficult because simple clinical variables such as older age and delay to therapy that predict poorer outcome are more prevalent among patients with diabetes. Other potential mechanisms of the excess mortality may be more subtle and include decreased success rate of lytic therapy, larger MI and a greater complication rate from primary PTCA. The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO –1) Angiographic Study provides some insight interaction of diabetes with clinical variables as well as angiographic variables after fibrinolytic therapy (Figure 7). After correction, diabetes conferred a 2-fold excess mortality risk over a nondiabetic population.

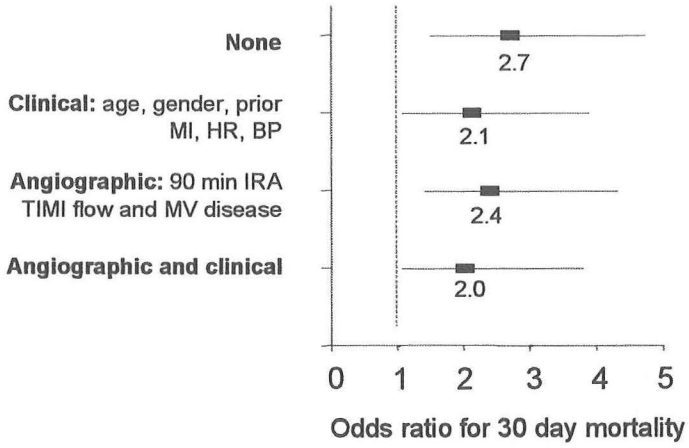

Figure 7. Effect of diabetes on 30 day mortality and interaction with clinical variables, angiographic variables, or both. "None" indicates the raw excess risk of diabetes. "Clinical" indicates the risk after correction for the clinical variables, and "angiographic" is the risk after correction for angiographic covariates. Redrawn from reference 86.

Table 8. Summary of results from Fibrinolytic Therapy Trialists Collaborative (reference 23).

	Number of patients assigned to a treatment group		Number of deaths, 0 – 35 days (%)		Benefit per 1,000 patients treated (± s.d.)
	Fibrinolytic	Control	Fibrinolytic	Control	
Diabetes	2236	2260	303 (13.6%)	391 (17.3%)	37 ± 11
No diabetes	19423	19424	1697 (8.7%)	1981 (10.2%)	15 ± 3

Fibrinolytic therapy

The immediate goal of fibrinolytic therapy, restoration of patency in the infarct related artery, is equally likely to be achieved among patients with diabetes and without diabetes (86). Since vessel patency predicts outcome, this observation indirectly supports the use of thrombolytic therapy among diabetics. Direct support for the use of fibrinolytic agents comes from the Fibrinolytic Therapy Trialists Collaborative Group which summarized the results from all nine prospective randomized trials of fibrinolytic therapy involving over 1000 patients. Among the aggregate 58,600 patients, 4,496 had diabetes. The proportional reduction in mortality due to fibrinolytic therapy among diabetics tended to be greater than among

nondiabetics. The calculated absolute benefit of treatment, lives saved per 1,000 patients treated, was greater for patients with diabetes.

Insulin and glucose

When the myocardium is exposed to physiological concentrations of long chain fatty acids, glucose, lactate and ketones, the dominant source of energy production is through oxidation of long chain fatty acids with lesser contributions from lactate and ketones. The source of energy could influence outcome after ischemia through at least two well-investigated mechanisms. First, although glucose makes only a minor contribution to total energy production, ATP derived from substrate level phosphorylation during glycolysis is preferentially available for membrane-bound ion pumps. During or after ischemia it is conceivable that disruption of the intracellular ionic environment is corrected more rapidly when glucose is available for metabolism. Second, complete oxidation of long chain fatty acids produces less ATP per unit of oxygen consumed than does oxidation of carbohydrates. Although this difference is negligible for a well-oxygenated myocardium it is possible that under conditions of limited oxygen delivery improved myocardial efficiency may improve recovery.

Since at least the early 1960s there has been interest in improving left ventricular function after MI by modifying intermediary metabolism, particularly by stimulating glucose oxidation. There is some evidence for benefit by driving glucose oxidation among patients without diabetes (17, 22). In the Diabetes Insulin Glucose Acute Myocardial Infarction trial (DIGAMI, 620 patients, 80% with type 2 diabetes) patients with myocardial infarction were assigned to either intense combined glucose and insulin infusion for 24 hours followed by subcutaneous insulin, or usual care. The remainder of patient management was up to the physician and included fibrinolysis, β blockers and aspirin in the majority of patients. Mortality was reduced by 30% in the intensive treatment group at 1 year, and the survival advantage persisted. An important observation may be that the benefit of insulin is most apparent in low risk patients, that is, young with no prior MI or heart failure (Figure 8). Perhaps an early switch to insulin has a much greater benefit than has been appreciated.

This trial examined a complex treatment strategy which involved aggressive insulin therapy plus discontinuation of other hypoglycemic drugs during both the periinfarct and late period. Hence, the mechanism of the benefit could include reduced infarct size, reduced risk from oral hypoglycemic drugs during the periinfarct period, improved metabolic control late after MI, or other factors. Since the greatest benefit appeared to have been in patients not previously on insulin, the discontinuation of oral hypoglycemics may have played a role. The limitations of this study include its relatively small size and heterogeneous population which included type 1 and type 2 diabetes. Nevertheless, 80% of the patients had type 2 diabetes and this is one of the few trials to explicitly enroll only patients with diabetes. Since the magnitude was substantial and there is animal and theortical support

Primary coronary artery angioplasty for acute myocardial infarction

The PAMI trial confirmed the high in hospital risk for diabetics. Interestingly, the mortality rate for patients randomized to PTCA was 0% compared to 20.8% among patients managed with thrombolytic therapy. One should hastily emphasize that these are small numbers of patients analyzed in a retrospective manner. Together with the results from thrombolytic therapy trials, these results indicate that prompt reperfusion therapy is critical for patients with diabetes.

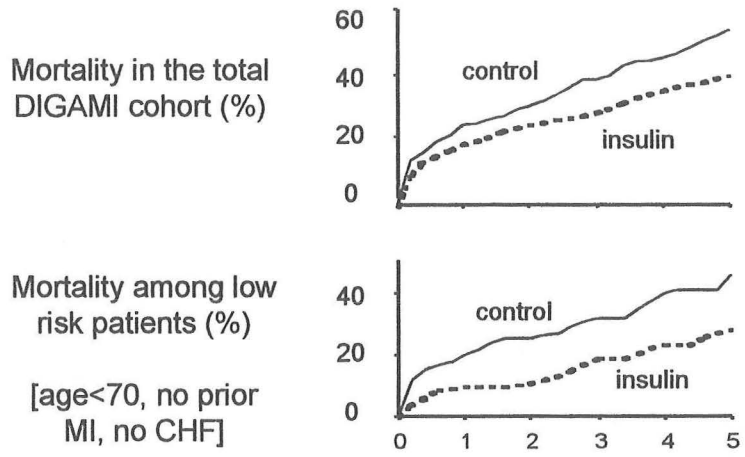

Figure 8. Long term mortality curves among patients in the total DIGAMI cohort (top panel) compared to patients identified prior to randomization as low risk (bottom panel). Among the total DIGAMI cohort, absolute reduction in risk was 11%, p = 0.011. Among the low risk patients, absolute reduction in risk was 15%, p = 0.004.

LEFT VENTRICULAR DYSFUNCTION

Left ventricular dysfunction among patients with type 2 diabetes is often multifactorial and may include influences from left ventricular hypertrophy due to hypertension, prior unrecognized MIs, ongoing silent ischemia, endothelial dysfunction, collagen deposition, and abnormal substrate oxidation. Hence, the term "diabetic cardiomyopathy" is imprecise and perhaps misleading because of the depressingly negative connotations of cardiomyopathy. The combination of depressed left ventricular systolic function and type 2 diabetes should be evaluated by cardiac catheterization.

ACE inhibitors are better studied than most drugs for heart failure, and some randomized trials of ACE inhibitors in left ventricular dysfunction have reported a diabetic cohort. Subset analysis found similar benefits of ACE inhibitors for patients with and without diabetes. These drugs are indicated when systolic dysfunction is present, and may also benefit patients with diastolic dysfunction. When left-ventricular dysfunction is evident in a patient with type 2 diabetes, significant coronary artery disease must be excluded, and an ACE inhibitor is strongly indicated. Unfortunately, however, patients with type 2 diabetes and mild renal insufficiency are at increased risk of hyperkalemia in the presence of ACE inhibitors.

Table 9: Effect of enalapril on the risk of death or hospitalization in the Study of Left Ventricular Dysfunction. From reference 75.

Treatment trial			Prevention trial	
DM	No DM		DM	No DM
67%	54%	Placebo	37%	22%
55%	46%	Enalapril	27%	19%

CORONARY ANGIOPLASTY

The initial success of PTCA in patients with diabetes is not different from the general population (Figure 9). However, the risk of restenosis, after either conventional balloon angioplasty (79) or intracoronary stenting, was initially thought to be increased among patients with diabetes. One report (69) suggested that diabetes increases the rate of new coronary lesions as a consequence of entering a coronary artery for angioplasty. A number of reports confirm the excess restenosis rate after balloon angioplasty (6), but the picture after stenting is less clear. In some studies diabetics had a much higher risk of restenosis after stenting, but Van Belle (83) recently reported the opposite: the restenosis rate was 25%among diabetics and 27% among nondiabetics. On the other hand, direct intravascular ultrasound studies indicate that the reason for exaggerated restenosis is due to neointimal hyperplasia (40).

Table 10. Effect of abciximab on 6 month event rates among patients with diabetes. The number of patients experiencing each event is shown. TVR, target vessel revascularization.

	death	MI	TVR	Death, MI or TVR
Stent + placebo (n=173)	3	19	28	43
Stent + abciximab (n= 162)	1	10	13	21
p, abciximab vs placebo	0.35	0.11	0.02	0.005

Overall survival after PTCA among diabetics is worse than for patients without diabetes. The reasons are not clear, but higher rates of restenosis, more diffuse disease leading to incomplete revascularization, impaired sensation of recurrent ischemia, and other factors may contribute.

The platelet IIb/IIIa receptor antagonists have received intense evaluation because of their ability to reduce the frequency of acute coronary thrombotic events during and after percutaneous revascularization. Recently, a IIb/IIIa blocker, abciximab, was reported to have a surprising effect in patients with diabetes undergoing stenting. In that study a subset of patients with diabetes were randomly assigned to stent plus placebo, stent plus abciximab or balloon angioplasty plus abciximab (Table 10).

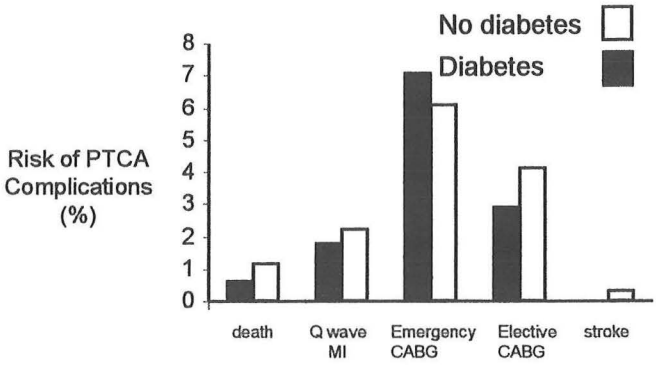

Figure 9. Risk of complications related to PTCA. The risk of death, Q wave MI, emergency CABG, nonemergency or elective CABG and stroke among patient with diabetes and without diabetes are compared. There were no significant differences between the groups. Results from the BARI trial.

CORONARY ARTERY BYPASS SURGERY

The procedural success rate for bypass surgery among patients with diabetes is identical to those patients without diabetes. Perioperative mortality rates are not increased among patients with diabetes after bypass graft surgery, although the risk of wound infections is increased, and some surgeons avoid bilateral IMA grafts for this reason (3). Hospital stays tend to be longer for patients with diabetes after CABG (3). For the average patient (diabetic or not) the standard coronary artery bypass operation includes one internal mammary artery bypass (IMA). The primary benefit of an IMA, of course, is improved long term patency compared to reversed saphenous vein grafts. This benefit is at least as great among diabetics compared to nondiabetic patients (60). Overall, not using an IMA in a patient without diabetes generates about the same subsequent risk as bypass surgery including one IMA in a patient with diabetes.

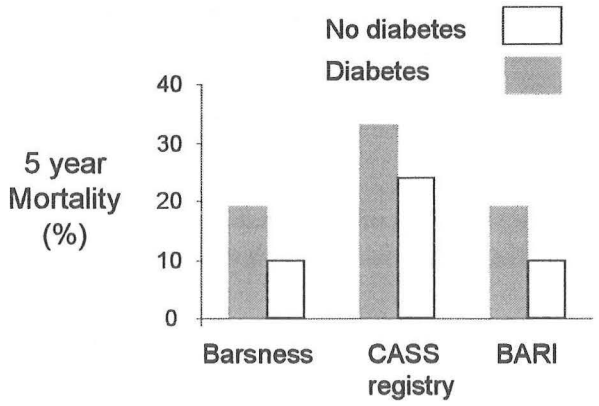

Figure 10. Five year CABG mortality rates. From references 8, 9, and 10.

The long term prognosis is unfortunately (Figure 10) much worse among diabetics which may be a consequence of inexorable progression of vein graft disease in the setting of hyperglycemia and dyslipidemia. For example, in a retrospective study from the Duke data base (8), unadjusted mortality after bypass surgery was significantly greater among diabetics than among nondiabetics. Even after adjustment for age, heart failure, severity of coronary disease and comorbid illnesses, the adverse impact of diabetes persisted. Similar observations were reported from the Coronary Artery Surgery Study Registry (9). In that report which focused on 317 patients with diabetes older than 65 years, the authors emphasized that elderly patients with diabetes benefit from bypass surgery. Nevertheless, diabetes remained an independent predictor of mortality die after CABG. In the Bypass Angioplasty Revasularization Investigation (BARI), diabetes also was associated with a higher mortality rate after CABG (10).

Among the many trials with similar design (38), the BARI trial compared survival after bypass graft surgery or angioplasty in 1829 patients with multivessel disease suitable for revascularization by either method. In that study, 19% of patients were diabetic, a rather large proportion compared to many randomized trials. Patients with left main coronary artery disease, acute coronary syndromes or prior revascularization were excluded. Notably, recruitment was from 1988 to 1991, prior to widespread availability of stents or IIb/IIIa inhibitors. Associated risk factors were significantly worse for the diabetic patients (compared to nondiabetic patients in the trial) and included higher triglycerides, higher prevalence of congestive heart failure, and more 3 vessel disease. However, there were no significant differences in risk factors between the diabetic patients assigned to surgery compared to those assigned to PTCA. The primary endpoint was mortality at 5 years.

Table 11. Outcomes in the randomized arm of the BARI trial (8).

		Cardiac death rate	
Diabetic patients	n	n	%
CABG with IMA	140	4	2.9
CABG, SVG only	33	6	18.2
PTCA	170	35	20.6
Others			
CABG with IMA	586	27	4.6
CABG, SVG only	130	7	5.4
PTCA	734	35	4.8

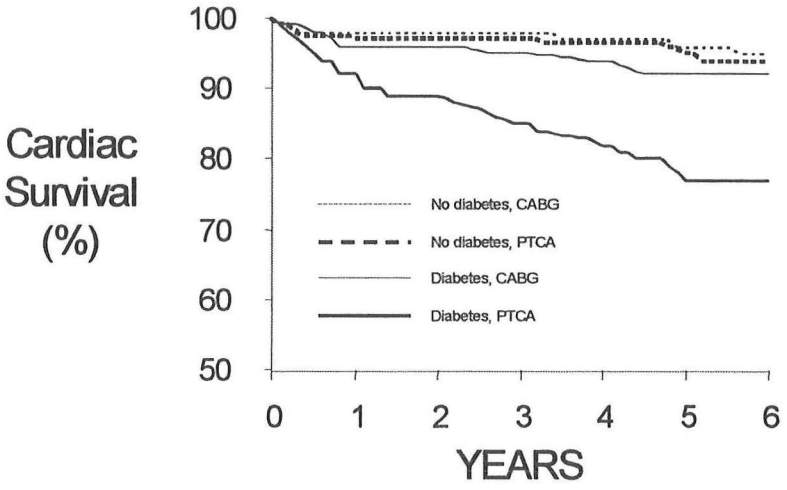

Figure 11. Survival in the BARI trial. 1829 patients with multivessel coronary artery disease wer randomized to CABG or PTCA. Results are based on intention-to-treat analysis (from reference 8).

Diabetic patients had a lower 5-year survival than non-diabetic patients, regardless of the treatment group, confirming earlier observations. Significantly, within the diabetic subgroup, the survival was 80.6% among patients assigned to bypass surgery but only 65.5% among patients assigned to angioplasty. This superiority of CABG has also been supported in some observational studies (27).

The poorer outcomes have been attributed to three factors. First, in patients with diabetes, disease is more extensive and revacularization by PTCA more difficult. Second, the rate of progression of coronary disease may is more rapid in patients with diabetes. Third, restenosis may be more difficult to detect in patients with diabetes mellitus (because of altered symptoms) and therefore the risk of USA or myocardial infarction may be increased.

The difference in outcome between CABG and PTCA in this trial generated controversy which remains unresolved. One important question is the consistency of these findings with other trials. Similar to BARI, the Coronary Angioplasty versus Bypass Revascularization Investigation trial reported that patients with diabetes had better outcomes with bypass surgery. By contrast, the Emory Angioplasty Surgery Trial did not find a difference between outcomes among diabetics assigned to surgery compared to PTCA. The BARI registry of eligible patients not randomized also did not demonstrate the survival advantage of CABG (Table 12). The reasons for these discrepancies are unclear. Interventionalists may be quite adept at identifying subtle features of the angiogram or other factors that predict poor outcome. Surgery may be preferred with diffuse small vessel mulilesion coronary disease.

Table 12. Comparison of outcomes for patients with diabetes: results from BARI, Duke, and BARI eligible but not randomized patients.

	PTCA	CABG	PTCA survival	CABG survival
Duke (9)	19%	81%	76%	74%
BARI	50%	50%	66%	81%
BARI eligible, not randomized	61%	39%	86%	85%

CONCLUSIONS

Most of the evidence for clinical decisions involving patients with type 2 diabetes and coronary disease is derived from 1) uncontrolled observational studies, 2) small retrospective subgroup analysis of larger trials, 3) extrapolation of results from trials involving type 1 diabetes, or 4) randomized trials of relatively healthy patients with type 2 diabetes. There is some evidence that therapies for type 2 diabetes may influence the consequences of coronary artery disease, but control of hyperglycemia (rather than the therapy) is the cornerstone. Patients with type 2 diabetes may respond differently to conventional therapy compared to nondiabetic patients.

Key points:

- After coronary artery disease is evident, the prognosis for patient with type 2 diabetes mellitus is much worse than for patients without diabetes.
- Risk factor modification should include reasonably aggressive glycemic control and treatment of any dyslipidemia.
- Widely–used therapies including beta blockers, angiotensin converting enzyme inhibitors, and calcium channel blockers are appropriate and effective for patients with type 2 DM. For some of these therapies, notably beta blockers and angiotensin converting enzyme inhibitors, the benefit may be substantially greater among patients with diabetes than among nondiabeteic patients.
- The immediate procedural success rates for acute interventions – thrombolytic therapy, angioplasty, bypass surgery – are equivalent among patients with type 2 diabetes compared to a nondiabetic population. However, the long-term outcome after acute interventions is uniformly worse.
- Management of type 2 diabetic patients with acute myocardial infarction should include rapid administration of fibrinolytics or primary PTCA, aspirin, and early ß-blockade, all according to conventional protocols, except that at least 325 mg of aspirin should be given initially. Tight glucose control with insulin is likely beneficial if maintained throughout the post infarct period.
- Revascularization by either angioplasty or by bypass surgery is appropriate for patients with type 2 diabetes and poorly controlled angina. However, CABG may be preferred for patients with multilesion, multivessel coronary disease or three vessel disease plus depressed left ventricular function.

References

1. Abaci A, Oguzhan A, Kahraman S, et al. Effect of diabetes mellitus on formation of coronary collateral vessels. **Circulation** 1999; 99: 2239-2242.

2. Abraira C, Colwell J, Nuttall F, et al. Cardiovascular events and correlates in the Veterans Affairs diabetes feasibility trial. **Arch Intern Med** 1997; 157: 181-8.

3. Accola KD, Jones EL, Craver JM, et al. Bilateral mammary artery grafting: avoidance of complications with extended use. **Ann Thorac Surg** 1993; 56: 872-78.

4. Anonymous. 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; 352: 837-53.

5. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. **BMJ** 1994; 308: 81-106.

6. Aronson D, Bloomgarden Z, Rayfield EJ. Potential mechanisms promoting restenosis in diabetic patients. **J Am Coll Cardiol** 1996; 27: 528-35.

7. Balkau B, Shipley M, Jarrett RJ, Pylora. High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men: 20 year follow-up in the Whitehall study, the Paris prospective study, and the Helsinki policemen study. **Diabetes Care** 1998; 21: 360-7.

8. BARI Investigators. Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease: the Bypass Angioplasty Revascularization Investigation (BARI). **Circulation** 1997; 96: 1761-69.

9. Barsness GW, Peterson ED, Ohman EM, et al. Relation between diabetes mellitus and long-term survival after coronary bypass and angioplasty. **Circulation** 1997; 96: 2551-2556.

10. Barzilay JI, Kronmal RA, Bittner V, et al. Coronary artery disease and coronary artery bypass grafting in diabetic patients aged >=65 years (report from the Coronary Artery Surgery Study [CASS] registry). **Am J Cardiol** 1994; 74: 334-39.

11. Braun S, Boyko V, Behar S. Calcium antagonists and mortality in patients with coronary artery disease: a cohort study of 11,575 patients. **J Am Coll Cardiol** 1996; 28: 7-11.

12. Chen J, Marciniak TH, Radford MJ, et al. Beta blocker therapy for secondary prevention of MI in elederly diabetic patients. **J Am Coll Cardiol** 1999; 34: 1388-94.

13. Crutchley DJ, McPhee GV., Terris MF, Canossa-Terris MA. Levels of three hemostatic factors in relation to serum lipids. Monocyte procoagulant activity, tissue plasminogen activator, and type-1 plasminogen activator inhibitor. **Arteriosclerosis** 1989; 9: 934-9.

14. Deacon SP, Karunanayake A, Barnett. Acetbutolol, atenolol and propranolol and metabolic response to acute hypoglycemia in diabetes. **BMJ** 1977; 2: 1255-7.

15. Diabetes Control and Complications Trial Research. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. **N Engl J Med** 1993; 329: 977-86.

16. Diabetes Control and Complications Trial Research. Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. **Am J Cardiol** 1995; 75: 894-903.

17. Diaz R, Paolasso EC, Piegas LS. Metabolic modulation of acute myocardial infarction: the ECLA glucose-insulin-potassium pilot trial. **Circulation** 1998; 98: 2227-34.

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 Metab Res Suppl** 1985; 15: 41-6.

19. Estacio RO, Jeffers BW, Hiatt WR, et al. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. **N Engl J Med** 1998; 338: 645-52.

20. ETDRS Investigators. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. **JAMA** 1992; 268: 1292-300.

21. Ewing DJ, Boland O, Neilson JM, et al. Autonomic neuropathy, QT interval lengthening, and unexpected deaths in male diabetic patients. **Diabetologia** 1991; 34: 182-85.

22. Fath-Ordoubadi F, Beatt KJ. Glucose-insulin-potassium in acute myocardial infarction. **Lancet** 1999; 353: 68-69.

23. Fibrinolytic Therapy Trialists' Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. **Lancet** 1994; 343: 311-22.

24. Garratt KN, Brady PA, Hassinger NL, et al. Sulphonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. **J Am Coll Cardiol** 1999; 33: 119-124.

25. Giugliano D, Acampora R, Marfella R, et al. Metabolic and cardiovascular effects of carvedilol and atenolol in NIDDM and hypertension: a randomized, controlled trial. **Ann Intern Med** 1997; 126: 955-59.

26. Grundy SM. Small LDL, atherogenic dyslipidemia, and the metabolic syndrome. **Circulation** 1997; 95: 1-3.

27. Gum PA, O'Keefe JH, Borkkon AM, et al. Bypass surgery versus coronary angioplasty for revascularization of treated diabetic patients. **Circulation** 1997; 96: (suppl2) II7-II10.

28. Gundersen. Timolol treatment after myocardial infarction in diabetic patients. **Diabetes Care** 1983; 6: 285-90.

29. Heart Outcomes Prevention Evaluation Study Investigators, Ryden L, Hamsten A, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. **N Engl J Med** 2000; 342: 145-153.

30. Inzucchi SE, Maggs DG, Spollet GR, et al. Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. **N Engl J Med** 1998; 338: 867-872.

31. ISIS-2 Collaborative Group. ISIS-2 Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarctions: ISIS-2. **Lancet** 1988; 2: 349-60.

32. Jarrett RJ, Shipley MJ. Type 2 (non-insulin-dependent) diabetes mellitus and cardiovascular disease--putative association via common antecedents; further evidence from the Whitehall Study. **Diabetologia** 1988; 31: 737-40.

33. Jensen-Urstad KJ, Reichard PG, Rosfors JS, et al. Early atherosclerosis is retarded by improved long-term blood glucose control in patients with IDDM. **Diabetes** 1996; 45: 1253-58.

34. Jeppesen J, Heln HO, Suadicani P, Gyntelberg F. Relation of high TG-low HDL cholesterol and LDL cholesterol to the incidence if ischemic heart disease: an 8-year follow-up in the Compenhagen Male Study. **Arterioscler Thromb Vasc Biol** 1997; 17: 1114-1120.

35. Jollis JG, Simpson RJ, Cascio WE, et al. The relation between sulfonylurea therapy, complicatioins and outcome for elderly acute myocardial infarction patients. **Am Heart J** 1998; 138: S376-S380.

36. Jonas M, Reicher-Reiss H, Boyko V, et al. Usefulness of beta-blocker therapy in patients with non-insulin-dependent diabetes mellitus and coronary artery disease. **Am J Cardiol** 1996; 77: 1273-77.

37. Kendall MJ, Lynch KP, Hjalmarson A, Kjekshus J. Beta-blockers and sudden cardiac death. **Ann Intern Med** 1995; 123: 358-67.

38. King SB, Lembo NJ, Weitnraub WS. A randomized trial comparing coronary angioplasty with coronary bypass surgery. **N Engl J Med** 1994; 331: 1044-50.

39. Kjekshus J, Gilpin E, Calli G, et al. Diabetic patients and beta-blockers after acute myocardial infarction. **Eur Heart J** 1990; 11: 43-50.

40. Kornowski R, Mintz GS, Kent KM, et al. Increased restenosis in diabetes mellitus after coronary interventions is due to exaggerated intimal hyperplasia. **Circulation** 1997; 95: 1366-69.

41. Koskinen P, Manttari M, Manninen V, et al. Coronary heart disease incidence in NIDDM patients in the Helsinki heart study. **Diabetes Care** 1992; 15: 820-25.

42. Krentz AJ. Insulin resistance. **BMJ** 1996; 313: 1385-9.

43. Kuusisto J, Mykkanen L, Pyorili K, Laakso M. NIDDM and its metabolic control predict coronary heart disease in the elderly subjects. **Diabetes** 1994; 43: 960-67.

44. Lager I, Smith U, Blohme G. Effect of cardioselective and non-selective beta-blockade on hypoglycaemic response in insulin-dependent diabetes. **Lancet** 1979; 1: 458-62.

45. Lam KSL, Cheng IKP, Janus ED, Pang RWC. Cholesterol-lowering therapy may retard the progression of diabetic nephropathy. **Diabetologia** 1995; 38: 604-09.

46. Langer A, Freeman MR, Josse RG, Armstrong PW. Metaiodo-benzylguanidine imaging in diabetes mellitus: assessment of cardiac sympathetic denervation and its relation to autonomic dysfunction and silent myocardial ischaemia. **J Am Coll Cardiol** 1995; 25: 610-18.

47. Leibowitz G, Cerasi E. Sulphonylurea treatment on NIDDM patients with cardiovascular disease: a mixed blessing. **Diabetologia** 1996; 39: 503-514.

48. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. **N Engl J Med** 1993; 329: 1456-62.

49. Litzelman DK, Slemenda CW, Langefeld CD, et al. Reduction of lower extremity clinical abnormalities in patients with non-insulin-dependent diabetes mellitus. **Ann Intern Med** 1993; 119: 36-41.

50. Mak KH, Moliterno DJ, Granger CB, et al. Influence of diabetes mellitus on clinical outcome in the thrombolytic era of acute myocardial infarction. GUSTO-I Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. **J Am Coll Cardiol** 1997; 30: 171-9.

51. Malmberg K, et al. Effects of metoprolol on mortality and late infarction in diabetics with suspected acute myocardial infarction. Retrospective data from two large studies. **Eur heart J** 1989; 10: 423-8.

52. Malmberg K, Ryden L, Efendic S. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI Study): effects on mortality at 1 year. **J Am Coll Cardiol** 1995; 26: 57-65.

53. Malmberg K for the DIGAMI Study Group. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. **BMJ** 1997; 314: 1512-15.

54. Mancini CBJ, Henry GC, Macaya C, et al. Angiotensin converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease: the TREND (Trial on Reversing Endothelia Dysfunction) Study. **Circulation** 1996; 94: 258-65.

55. Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncadiac surgery. **N Engl J Med** 1996; 335: 1713-20.

56. Manninen V, Tenkanen L, Koskinen P, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study: Implications from treatment. **Circulation** 1992; 85: 37-45.

57. Marchant B, Umachandran V, Stevenson R, Kopelman P. Silent myocardial ischaemia: role of subclinical neuropathy in patients with and without diabetes. **J Am Coll Cardiol** 1993; 22: 1433-37.

58. McVeigh G, Brennan G, Hayes R, Johnston D. Primary nitrate tolerance in diabetes mellitus. **Diabetologia** 1994; 37: 115-17.

59. Miles GA, Hunt R. Beta blockers and glucose control. **Drug Intell Clin Pharm** 1985; 19: 246-51.

60. Morris JJ, Smith LR, Jones RH. Influence of diabetes and mammary artery grafting on survival after coronary bypass. **Circulation** 1991; 84: (suppl):III275-84.

61. Moye LA, Pfeffer MA, Pfeffer MA, Wun CC. Uniformity of captopril benefit in the SAVE study: subgroup analysis. **Eur Heart J** 1994; 15: (supplB):2-8.

62. Nattrass M. Managing diabetes after myocardial infarction. **BMJ** 1997; 314: 1497.

63. Ohkkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes. **Diabetes Res Clin Pract** 1995; 28: 103-17.

64. O'Keefe JH Jr, Blackstone EH, Sergeant P, McCallister BD. The optimal mode of coronary revascularization for diabetics: a risk adjusted long term studye comparing coronary angioplasty and coronary bypass surgery. **Eur Heart J** 1998; 19: 1696-1703.

65. Pierce LR, Wysowski DK, Gross TP. Myopathy and rhabdomyolysis associated with lovastatin-gemfibrozil combination therapy. **JAMA** 1990; 264: 71-75.

66. Pyorala K, Pedersen TR, Kjekshus J, et al. Cholesterol lowering with simvastatin improvesprognosis of diabetic patients with coronary heart disease: a subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). **Diabetes Care** 1997; 20: 614-620.

67. Reaven GM, Chen YD, Jeppesen J, et al. Insulin resistance and hyperinsulinemia in individuals with small, dense low density lipoprotein particles. **J Clin Invest** 1993; 92: 141-146.

68. Reichard P, Nilsson B, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. **N Engl J Med** 1993; 329: 304-9.

69. Rozenman Y, Sapoznikov D, Mosseri M, et al. Long term angiographic follow-up of coronary balloon angioplasty in patients with diabetes mellitus: a clue to the explanation of the results of the BARI study. **J Am Coll Cardiol** 1997; 30: 1420-25.

70. Ryan TJ, Anderson JL., Antman EM. ACC/AHA guidelines for the management of patients with acute myocardial infarction: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). **Circulation** 1996; 94: 2341-50.

71. Sacks FM, Pfeffer MA, Moye LA. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. **N Engl J Med** 1996; 335: 1001-09.

72. Sandrone G, Mortara A, Torzillo D, et al. Effects of beta blockers (atenolol or metoprolol) on heart rate variability after acute myocardial infarction. **Am J Cardiol** 1994; 74: 340-45.

73. Schaper W, Buschmann I. Collateral circulation and diabetes. **Circulation** 1999; 99: 2224-2226.

74. Schwartz S, Raskin P, Fonseca, Graveline JF. Effect of troglitazone in insulin treated patientw with type II diabetes mellitus. **N Engl J Med** 1998; 338: 861-6.

75. Shindler DM, Kostis JB, Yusuf S, et al. Diabetes mellitus, a predictor of morbidity and mortality in the Studies of Left Ventricular Dysfunction (SOLVD) trials and registry. **Am J Cardiol** 1996; 77: 1017-20.

76. Smits P, Thien T. Cardiovascular effects of sulphonylurea derivatives: implications for the treatment of NIDDM? **Diabetologia** 1995; 38: 116-121.

77. Sowers JR, Epstein M. Diabetes mellitus and associated hypertension, vascular disease, and nephropathy. **Hypertension** 1995; 26: 869-79.

78. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. **Diabetes Care** 1993; 16: 434-44.

79. Stein B, Weintraub WS, Gebhart SP, et al. Influence of diabetes mellitus on early and late outcome after percutaneous transluminal coronary angioplasty. **Circulation** 1995; 91: 979-89.

80. Turner R, Cull C, Holman R. United Kingdom Prospective Diabetes Study 17: a 9-year update of a randomized, controlled trial on the effect of improved metabolic control on complications in non-insulin-dependent idabetes mellitus. **Ann Intern Med** 1996; 124: 136-145.

81. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes. **Lancet** 1998; 352: 854-865.

82. University Group Diabetes Program. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. VI. Supplementary report o n onfatal events in patients treated with tolbutamide. **Diabetes** 1976; 25: 1129-1153.

83. Van Belle E, Bauters C, Hubert E, et al. Restenosis rates in diabetic patients: a comparson of coronary stenting and balloon angioplasty in native coronary vessels. **Circulation** 1997; 96: 1454-60.

84. Watkins PB, Whitcomb RW. Hepatic dysfunction associated with troglitazone. **N Engl J Med** 1998; 338: 916-917.

85. Wei K, Dorian P, Newman D, Langer A. Association between QT dispersion and autonomic dysfunction in patients with diabetes mellitus. **J Am Coll Cardiol** 1995; 26: 859-63.

86. Woodfield SL, Lundergan CF, Reiner JS, et al. Angiographic findings and outcome in diabetic patients treated with thrombolytic therapy for acute myocardial infarction: the GUSTO-1 experience. **J Am Coll Cardiol** 1996; 28: 1661-69.

87. Zarich S, Waxman S, Freeman RT, et al. Effect of autonomic nervous system dysfunction on the circadian pattern of myocardial ischemia in diabetes mellitus. **J Am Coll Cardiol** 1994; 24: 956-62.

88. Zuanetti G, Latini R, Maggioni AP. Influence of diabetes on mortality in acute myocardial infarction: data from the GISSI-2 study. **J Am Coll Cardiol** 1993; 22: 1788-94.