



Reducing the impact of the diabetic heart's increased vulnerability to cardiovascular disease

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The relative impact of diabetes on cardiovascular mortality is steadily increasing. The manifestations of heart disease have an incidence several times higher in diabetic patients than in their nondiabetic counterparts. This is complicated by a specific risk factor complex (hypertension; dyslipidemia; and autonomic, platelet, and coagulation dysfunction) that requires incorporation into study design and routine therapeutics. The physiological specificity of diabetic cardiomyopathy is diastolic dysfunction. The inability to increase myocardial blood flow in response to ischemia even in the absence of overt heart disease is independently related to long- and short-term blood glucose control. This forms the rationale for aggressive metabolic management of acute events with insulin-glucose-potassium infusion, combined with therapeutic strategies such as preferential β -blockade with ACE inhibitor cover for the increased risk of heart failure in infarction, and the deployment of the same risk factor interventions as in nondiabetics, only to markedly tighter targets: blood pressure control $\leq 140/80$ mm Hg, platelet stabilizing and fibrinolytic therapy, lipid-lowering therapy, and revascularization of multivessel disease, preferentially with bypass surgery. However, all such strategies require urgent ongoing review in prospective clinical trials prestratified for diabetes, while patients themselves deserve better structured cooperation between diabetologists and cardiologists.

Keywords: diabetes mellitus; cardiovascular disease; myocardial metabolism; blood glucose; risk factor; angina pectoris; myocardial infarction; coronary intervention; heart failure; therapy

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Despite considerable improvement in the treatment of cardiovascular disease, a recent US survey by Gu et al¹ clearly shows that patients with diabetes mellitus have not benefited from this to the same extent as their nondiabetic counterparts. This survey makes it plain that the decline in heart disease mortality in the general US population is not paralleled by a similar decline in patients with diabetes mellitus. Reduction in cardiovascular risk factors and improvement in the treatment of heart diseases thus seem to be less effective in the diabetic population, with women being at a particular disadvantage. In actual fact, the relative impact of diabetes on cardiovascular mortality is steadily increasing. Several explanations may be advanced for the above.

First of all, there seems to be a misconception among cardiologists that diabetes is an infrequent, unexciting disease and, in any event, that it is usually "mild" and "easy to treat." In addition, cardiologists tend to focus more on therapeutic measures directed toward the cardiac manifestations of the condition, while not fully appreciating that it is also necessary to address the underlying metabolic disorder in order for the treatment of the cardiac disorder to fully achieve its goal. Such an attitude runs the risk of jeopardizing the outcome of the condition, since, if not properly managed, the metabolic disorder may cause unnecessary harm, thus contributing to the prevailing dismal prognosis of diabetic patients with cardiovascular disease. For their part, diabetologists have, over the years, made significant headway in the management of insulin-dependent diabetes mellitus and the risk of cardiovascular complications in non-insulin-dependent diabetes. However, despite undeniable progress, as reported for instance in the United Kingdom Prospective Diabetes Study (UKPDS),² many issues still remain unresolved. Therefore, in our opinion, the key to improved care for the diabetic population

is increased cooperation between diabetologists, who manage diabetic patients before the development of cardiovascular complications, and cardiologists, who come in at a more advanced stage of the disease.

A second explanation is that the true magnitude of this subgroup of patients may be underestimated, particularly in the context of interpreting the results of clinical trials. This is because the incidence of diabetes mellitus increases with age, and, since clinical trials often set an upper age limit, this effectively excludes many diabetics from inclusion—a factor that is exacerbated by the fact that patients with diabetes are more likely than nondiabetics to be excluded from clinical trials due to cardiovascular complications and renal dysfunction. Proof of this is provided by clinical

trials that show that the diabetic subgroup usually makes up 15% to 25% of all patients, a figure that is considerably lower than the incidence of diabetics in unselected populations of patients with cardiovascular disease. The same is true of cardiology practice, where diabetic patients are common, presenting themselves with angina pectoris, myocardial infarction, and congestive heart failure (CHF), with many requiring coronary revascularization.

So what conclusions can be drawn from this?

First of all, more knowledge is definitely needed on specifically tailored treatment for the diabetic patient with cardiovascular disease. Studies on accurately characterized diabetic patients with cardiovascular

SELECTED ABBREVIATIONS AND ACRONYMS

ACE	angiotensin-converting enzyme
ATLAS	Assessment of Treatment with Lisinopril And Survival study
BARI	Bypass Angioplasty Revascularization Investigation
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CAPPP	CAPtopril Prevention Project
CARE	Cholesterol And Recurrent Events trial
CHF	congestive heart failure
CONSENSUS	COoperative North Scandinavian ENalapril SURvival Study
DIGAMI	Diabetic patients receiving Insulin-Glucose infusion during Acute Myocardial Infarction study
ECLA	Estudios Cardiológicos Latino America
GIK	glucose-insulin-potassium
GISSI-3	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico III
GUSTO	Global Utilization of Streptokinase and TPA for Occluded arteries trial
HOT	Hypertension Optimal Treatment study
LIPID	Long-term Intervention with Pravastatin in Ischemic Disease trial
LVEF	left ventricular ejection fraction
NYHA	New York Heart Association
PAI-1	plasminogen activator inhibitor-1
PTCA	percutaneous transluminal coronary angioplasty
RESOLVD	Randomized Evaluation of Strategies for Left Ventricular Dysfunction
4S	Scandinavian Simvastatin Survival Study
SAVE	Survival And Ventricular Enlargement study
SHEP	Systolic Hypertension in the Elderly Program
SOLVD	Studies Of Left Ventricular Dysfunction
SYST-EUR	SYSTolic hypertension in elderly in EUROpe trial
UKPDS	United Kingdom Prospective Diabetes Study



disease, including precise information on how the condition was diagnosed and treated, are scarce. This is also the case for large clinical trials with prospective stratification of diabetic patients and precise data on antidiabetic treatment and metabolic characteristics, not to mention studies exclusively targeting diabetic populations. This means that many of the current therapeutic recommendations for diabetic patients with coronary artery disease (CAD) are based on retrospective subgroup analyses of clinical trials conducted without any particular characterization or stratification of the diabetic patients. This is astonishing in light of the increasing prevalence of diabetes mellitus in general and the increasing number of diabetic patients with manifestations of CAD in particular. There is a clear need for further research in this field.

Second, contributing factors to the unfavorable prognosis of diabetic patients with CAD have to be taken into account when considering therapy. These include widespread and diffuse CAD, microvascular dysfunction, decreased vasodilatory reserve, decreased fibrinolytic activity, elevated spontaneous platelet aggregability, an atherogenic lipoprotein profile, autonomic dysfunction, and coexisting diabetic cardiomyopathy. Metabolic factors also contribute to the poor prognosis, in particular decreased insulin production associated with increased insulin resistance, and increased and less efficient metabolism of free fatty acids. The effect of metabolic factors is further aggravated by the stress induced by worsening angina or heart failure, and the anxiety associated with impending myocardial infarction.

This article reviews some of the factors that contribute to rendering the heart of the diabetic patient vulnerable. It also looks at some of the preventive and therapeutic options that may be proposed to reduce the impact of cardiovascular disease in the diabetic subject.

EPIDEMIOLOGY

The worldwide prevalence of diabetes mellitus and, in particular, type 2 or non-insulin-dependent diabetes, which makes up about 90% of the diabetic population, is currently increasing. The reasons for this increase include the aging of the population, an increase in average body mass, and decreased demands on physical activity. Changing food habits also contribute, particularly in the developing world. The worldwide prevalence of diabetes mellitus in the adult population was estimated to be 4.0% in 1995, a figure that is expected to increase to 5.4% by the year 2025. Thus,

the number of diabetic patients is projected to rise from the 135 million reported in 1995 to reach about 300 million by the year 2025. A major part of this increase will occur in developing countries, from 84 to 228 million. However, a considerable rise is also to be expected in the developed world, from 51 to 72 million. In developed countries, the majority of diabetic subjects are 65 years or older, a pattern that should be even more pronounced in the future. In the developing world, the majority of diabetic subjects are and will continue to remain in the 45- to 65-year-old age-group.³

In type 2 diabetes, manifestations of atherosclerosis are frequently already present at the time of diagnosis. Conversely, approximately 20% of patients admitted to Swedish coronary care units for myocardial infarction have diabetes. A recent health survey⁴ reported that 22% of diabetic patients had seen a cardiologist during the previous 12 months and that up to 50% had cardiovascular disease. Type 2 diabetes, including the prediabetic period, is an important risk factor for atherosclerosis. The increasing prevalence of diabetes therefore suggests that a considerable increase in diabetes-related cardiovascular disease will take place in the near future.

In spite of therapeutic improvements, CHF continues to be an important problem in cardiology, and mortality and morbidity remain high. The current substantial hospitalization rates for CHF account for a sizable proportion of total health care expenditure. Possible links between diabetes mellitus and heart failure are therefore of considerable interest. The Framingham study⁵ was the first epidemiological study to demonstrate an increased risk of CHF in diabetic subjects. Compared with nondiabetic males and females, the estimated increase in the incidence of heart failure was multiplied by a factor of four and eight in young diabetic males and females, respectively. Ten percent of patients hospitalized for CHF in western Sweden had diabetes mellitus according to a retrospective survey.⁶ However, since this study excluded individuals over the age of 65 and only patients on insulin were classified as having diabetes, this number is an underestimate of the true proportion.

The large angiotensin-converting enzyme (ACE) inhibitor clinical heart failure trials offer somewhat less age-restricted data. For example, the proportion of subjects with diabetes was 23% in the COoperative North Scandinavian ENalapril SURvival Study (CONSENSUS)⁷ and 25% in Studies Of Left Ventricular Dysfunction (SOLVD).⁸ As studies are always carried out on selected

populations, these figures also need to be interpreted with caution. In the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) study,⁹ the prevalence of diabetes was 27% at the time of randomization. In this study, blood glucose was measured at baseline and the most recent diagnostic criteria for diabetes were applied, yielding a prevalence of 35%. The discrepancies observed between the different studies are due to several factors, principally age, etiology, severity of heart failure, and the definition of diabetes mellitus.

Reis et al¹⁰ evaluated specialty-related differences in the care and outcome of patients admitted to hospital for heart failure. They noted that as many as 38% of all patients had diabetes mellitus requiring pharmacological treatment. Recent Italian cross-sectional data¹¹ indicate a 30% prevalence of diabetes in an elderly heart failure population. The association with diabetes was independent of age, sex, blood pressure, body mass index, waist/hip ratio, and family history of diabetes. Interestingly, the incidence of diabetes, calculated over 3 years of follow-up, was 29% in heart failure patients initially free from this disease, compared with 18% in a group of matched controls. Multivariate analysis indicated that CHF independently predicted subsequent type 2 diabetes. A possible explanation is that heart failure increases the adrenergic drive, in turn resulting in an increase in free fatty acid oxidation and insulin resistance, thereby decreasing glucose oxidation and precipitating type 2 diabetes.

A population-based study of elderly patients¹² concluded that diabetes mellitus is an independent risk factor for heart failure and that the risk increases with severity of disease. Furthermore, multivariate adjustment showed that an increase in baseline HbA_{1c} of 1% increased the risk of developing heart failure by 15% in patients with and without known diabetes. This indicates that the independent risk for developing heart failure in diabetic patients may to some extent be mediated by poor metabolic control.

In summary, there is consistent epidemiological evidence that diabetes mellitus is frequent in a heart failure population and that diabetes and heart failure may be interrelated.

DIABETIC CARDIOMYOPATHY

Ever since the Danish internist Lundbäck proposed the concept in 1954,¹³ it has been customary to attribute

the increased susceptibility of diabetic patients to ischemic heart disease to a diabetes-specific form of myocardial disease termed "diabetic cardiomyopathy." Although the most common cause of death in diabetic patients is not cardiomyopathy but CAD, heart failure is more frequent in diabetic than in nondiabetic patients with myocardial ischemic injury. This does not seem to be due to more extensive myocardial damage, as many reports show that infarct size is no larger in diabetic than in nondiabetic patients.

Morphology

According to a recent extensive review by Hardin¹⁴ of the numerous investigations devoted to morphological alterations in the diabetic heart, the most consistent findings are myocyte hypertrophy, interstitial fibrosis, increased periodic acid-Schiff (PAS)-positive material, and intramyocardial microangiopathy. The fact that there are no lesions specific to diabetes suggests that the cause of diabetic cardiomyopathy may be found at a functional or biochemical level. The structural changes usually attributed to hypertension seem to exert a synergistic effect, which may have important implications for treatment in the light of the favorable effect of antihypertensive therapy in diabetic patients, as noted for instance in the Hypertension Optimal Treatment (HOT)¹⁵ study and UKPDS.²

Diastolic dysfunction

When a noninfarcted myocardial area is subjected to acute ischemia, the usual response is compensatory hyperkinesia, the purpose of which is to correct the ejection fraction as far as possible. The Global Utilization of Streptokinase and TPA for Occluded arteries (GUSTO) trial,¹⁶ which included more than 300 diabetic subjects in whom coronary angiograms were performed 90 minutes after thrombolysis, showed that there was no difference in global ejection fraction between diabetic and nondiabetic patients. In contrast, the compensatory hyperkinetic response in noninfarcted myocardium appears to be blunted in diabetic patients, resulting in decreased regional ejection fraction in noninfarcted myocardial areas. Follow-up of the GUSTO trial indicated that CHF was almost twice as frequent in the diabetic as in the nondiabetic cohort. This is consistent with findings of Stone et al,¹⁷ who reported a higher incidence of heart failure in diabetic patients despite smaller infarct sizes and ejection fractions similar to those in subjects without diabetes. In all, these findings are suggestive of impaired diastolic function, which appears to be the



most characteristic feature of diabetes-related myocardial disease. Several studies¹⁸ have established that CAD, even in its asymptomatic form, is more frequent in diabetics than nondiabetics, which may provide an explanation for the blunting of the compensatory hyperkinetic response to ischemia and the development of diastolic dysfunction. Diastolic dysfunction is an early sign of myocardial ischemia. Most studies¹⁹ reporting diabetic cardiomyopathy did not angiographically exclude coexistent CAD. This must clearly be a requirement in future studies.

Myocardial blood flow

Impaired endothelium-dependent vasodilation (endothelial dysfunction) is another factor liable to compromise myocardial blood flow or impair its ability to increase when required. Although endothelial dysfunction has been documented in both type 1 and type 2 diabetes, its mechanism is not fully understood. Diabetic patients have a reduced myocardial flow reserve compared with matched controls even in the absence of overt heart disease. Acute hyperglycemia may impair endothelium-derived vasodilation in healthy humans. The inability to increase myocardial blood flow is independently related to long-term blood glucose control, but not to age, blood pressure, or blood lipid profile.²⁰ Accordingly, it may be assumed that elevated blood glucose by itself plays a considerable role in the impaired vascular response, thus contributing to the lack of hyperkinetic response and the diastolic dysfunction seen in diabetes mellitus. This provides a rationale for treatment aiming at strict glucose control in order to reduce cardiovascular events in the diabetic population.

Metabolic aspects

In an excellent review, Rodrigues et al²¹ suggest that metabolic factors may play a fundamental role in the development of myocardial dysfunction unrelated to macrovascular disease in diabetic patients. In addition to hyperglycemia, diabetes is characterized by an increased turnover of free fatty acids, which leads to increased myocardial oxygen utilization and enhanced intracellular accumulation of intermediates. This results in a range of various deleterious effects such as promotion of intracardiac conduction disturbances and arrhythmias, interference with adenosine triphosphate-dependent ion pumps, and increased α_1 -adrenergic response. As a result, intracellular calcium is mobilized, causing calcium overload and contractile dysfunction. The increase in free fatty

acids inhibits glucose transport and metabolism independently of the effects of insulin deficiency. Increased levels of citrate, produced by free fatty acid oxidation, inhibit phosphofructokinase, leading to decreased glycolysis and promoting glycogen synthesis. Impaired glucose oxidation also leads to lactic acid accumulation, which further promotes the degradation of free fatty acids.

In summary, diabetes-related myocardial dysfunction—in other words, diabetic cardiomyopathy—does exist and has important clinical implications. It is characterized by the absence of compensatory response to myocardial ischemia or injury, and early impairment of diastolic function. The pathophysiological mechanisms, which are not yet fully elucidated, are multifactorial, and include metabolic and vascular components. This suggests that interventions aimed at reducing hyperglycemia and increased free fatty acid oxidation, eg, through intensive insulin treatment, may be beneficial. Moreover, diabetes and hypertension appear to exert a synergistic action on the development of structural myocardial changes. This may explain why vigorous treatment of hypertension is of particular value in the diabetic patient.

AUTONOMIC DYSFUNCTION

Cardiac autonomic imbalance is a common consequence of diabetes. One of its effects is decreased or even abolished perception of ischemic pain. Silent ischemia may cause asymptomatic myocardial injury, with subsequent development of heart failure. Some studies indicate that silent ischemia is more frequent in diabetic patients than in their nondiabetic counterparts, but this is not a completely consistent finding.²² An increase in the pain perception threshold following the onset of ST-segment depression during exercise-induced myocardial ischemia has been reported in some diabetic patients. These patients may therefore be insensitive to anginal chest pain as a warning sign of myocardial ischemia, thereby exposing their hearts to an increased risk of injury. Painless myocardial infarction has been related to diabetic autonomic dysfunction. Atypical chest discomfort as an expression of myocardial ischemia is more frequent in patients with diabetes mellitus than in those without.

Even more important may be the effects of decreased vagal tone. Diabetic patients with disturbed autonomic function have a higher heart rate than nondiabetic

patients as a result of predominant parasympathetic dysfunction preceding the involvement of the sympathetic system.²³ Tachycardia increases myocardial oxygen demand and, as diastole is shortened, decreases myocardial blood flow duration. Impairment of vagal tone may also result in decreased heart rate variability, which is of prognostic importance since it is associated with increased risk of sudden cardiac death.

PROTHROMBOTIC FACTORS

Diabetes mellitus impairs platelet function by acting on various platelet activators, which results in increased platelet aggregation. Furthermore, release of platelet factor 4 and synthesis of thromboxane A₂ are increased in diabetic patients. Glycosylation of the glycoprotein IIb/IIIa (GPIIb/IIIa) receptor induces an increase in the binding of fibrinogen to the receptor.²⁴ This may explain recent observations²⁵ of a particularly favorable effect of glycoprotein receptor antagonists in diabetic patients.

Diabetic patients are characterized by a concomitant increase in fibrinogen concentration and decrease in fibrinolytic activity. Although levels of tissue plasminogen activator are usually normal or even somewhat increased, its activity is decreased. Two reasons may be invoked to explain this: increased concentration of plasminogen activator inhibitor-1²⁶ and/or glycosylation of plasminogen.²⁴

To summarize, as a result of these disturbances in platelet function and the coagulation cascade, diabetic patients are at higher risk of developing thrombotic occlusions. Furthermore, the spontaneous lysis of clots may also be considerably compromised in these patients. The diabetic patient with acute coronary syndromes therefore has a special need for efficient platelet-stabilizing and fibrinolytic therapy.

CORONARY RISK FACTORS AND THE DIABETIC PATIENT

Hypertension

Up to 70% of adults with type 2 diabetes have hypertension, and several prospective studies indicate that an increase in systolic blood pressure of 10 mm Hg increases the risk of cardiovascular events by 20%. Placebo-controlled trials have convincingly demonstrated the efficacy of antihypertensive treatment in reducing the risk of cardiovascular events in both dia-

betic and nondiabetic subjects (for a review see reference 27). Thus, the Systolic Hypertension in the Elderly Program (SHEP)²⁸ showed a twofold absolute risk reduction with chlorthalidone-based and atenolol-supplemented antihypertensive therapy in elderly type 2 diabetic patients compared with nondiabetic subjects. The SYSTolic hypertension in elderly in EUROpe trial (SYST-EUR)²⁹ recently reported similar findings with the calcium antagonist nitrendipine. The HOT study recently confirmed that diabetic patients benefited more from intensive blood pressure reduction than nondiabetic patients. Treatment in HOT was initiated with the dihydropyridine calcium antagonist felodipine and supplemented by an ACE inhibitor and a β -blockers in case of insufficient blood pressure control. The fundamental importance of tight blood pressure control in patients with type 2 diabetes was further emphasized by the recently published UKPDS study,³⁰ which indicated that β -blocker- and captopril-based treatment were equally effective in the prevention of macrovascular events. Furthermore, this study also showed, for the first time, the efficacy of such treatments in preventing microvascular events. However, compared with patients treated with atenolol, patients allocated to captopril treatment had lower HbA_{1c} values over the initial 4 years of follow-up and required less additional glucose-lowering treatment during the end of the study. A subgroup analysis from the recent CAPtopril Prevention Project (CAPP) study³¹ indicated that captopril-based treatment was more effective than β -blocker- and diuretic-based treatment in reducing cardiovascular events in diabetic subjects. Interestingly, captopril-treated nondiabetic patients had a 20% lower incidence of new diabetes than patients allocated to conventional treatment. The general impression that arises from these studies is that the target blood pressure should be low, of the order of 140/80 mm Hg or probably even lower in diabetic subjects. In order to accomplish this goal, multiple drug therapy is often needed. In the UKPDS study,³⁰ for example, almost one third of the intensively treated patients were at least on three different drugs.

A point of contention is whether calcium antagonists are harmful in the treatment of hypertension in diabetic patients, as ACE inhibitors have been shown to be superior to calcium antagonists in two head-to-head comparisons.^{32,33} At present, however, there is no convincing evidence to support this. On the contrary, it seems that ACE-inhibitor therapy, and possibly also β -blocker therapy, protect the diabetic patient from cardiovascular events beyond the effect of blood-pressure lowering. Thus, it is suggested that the



STUDY	Risk reduction (%)	Risk reduction (%)	Risk reduction (%)	Risk reduction (%)	Meta-analyses	Meta-analyses
	primary outcome no DM	primary outcome DM	combined end point† no DM	combined end point† DM	risk reduction (%) combined end point† no DM	risk reduction (%) combined end point† DM
4S ³⁹	30	43 (NS)	34	55		
CARE ⁴⁰	26	13 (NS)	26	13 (NS)	29 (18 to 39)	29 (-3 to 36)
LIPID * ⁴¹	24	Not given	25	19 (NS)		

Table I. Effect of lipid lowering in patients with or without diabetes (DM) in large secondary prevention statin trials.

*Data are given for the total patient cohort, since patients with diabetes were not characterized separately.

†Combined end point, CHD-death, or nonfatal myocardial infarction.

drugs of choice for first-line use in diabetic patients with hypertension are the ACE inhibitors, β -blockers, and diuretics, while calcium antagonists should only be considered following failure to fully control blood pressure by other means.²⁷

Dyslipidemia

Diabetic dyslipidemia is characterized by hypertriglyceridemia and decreased high-density lipoprotein (HDL) cholesterol levels. Hypertriglyceridemia is generally two to three times more frequent in the diabetic than in the nondiabetic population. The same is true for low HDL levels. There are strong indications that hypertriglyceridemia is an independent risk factor for cardiovascular disease in diabetic patients in whom low-density lipoprotein (LDL) levels are relatively low, as is the case in nondiabetics. Type 2 diabetic patients also have an increased proportion of small dense LDL particles compared with normoglycemic individuals. Besides the altered LDL composition, there is also firm evidence of increased oxidative stress in type 2 diabetes. In diabetic patients, LDL is more often glycosylated and therefore more likely to be oxidized, thus increasing the atherogenic risk in these patients, since oxidized LDL is more atherogenic than nonoxidized LDL.³⁴

So far, no trial has addressed the effect of lipid lowering on hard clinical end points specifically in patients with type 2 diabetes. Available data are derived from subgroup analyses of clinical trials. The American Diabetes Association³⁵ currently recommends active pharmacological treatment in diabetic patients without known cardiovascular disease when the LDL level is 3.4 mmol/L, and in those with cardiovascular disease when the LDL level is 2.6 mmol/L. Similar levels are also given in the guidelines of the European Society of Cardiology.³⁶

Previous primary prevention trials only included small proportions of patients with type 2 diabetes. In trials that focused on LDL reduction (eg, with statins), it seems that diabetic patients benefited as much as the overall study population.³⁷ As regards fibrates, the Helsinki Heart study³⁸ showed promising data in the diabetic subgroup; however, the numbers were small and the overall trend toward increased total mortality makes these findings difficult to interpret.

Several primary prevention studies including thousands of patients with diabetes are currently under way with different agents. The large secondary prevention studies, such as the Scandinavian Simvastatin Survival Study (4S),³⁹ the Cholesterol And Recurrent Events (CARE) trial,⁴⁰ and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial⁴¹ are summarized in *Table I*. Although the results vary somewhat, they are consistent. A meta-analysis showed that risk reduction for patients with and without diabetes was of the same magnitude, 29%, but since the event rate is higher in diabetic cohorts, the absolute benefit from intensive lipid lowering is greater in diabetics.

REVASCULARIZATION

It is well known that life expectancy is decreased in diabetic patients having undergone percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG), compared with their nondiabetic counterparts.

No randomized trials have been performed to check whether either of these two coronary interventions actually improves the long-term prognosis in diabetic patients. The available information is therefore based on observational studies and registry data.

According to the findings of the Bypass Angioplasty Revascularization Investigation (BARI),⁴² the 5-year mortality in diabetic patients with ischemic heart disease and 2- or 3-vessel disease was 35% in patients randomized to PTCA, and significantly less, 19%, in those randomized to CABG. These findings strongly suggest that CABG should be preferred over PTCA in diabetic patients with multivessel disease. In a two-center database study⁴³ totaling 15 809 patients (including patients with 1- to 3-vessel disease) having undergone either PTCA or CABG as initial revascularization procedure, 1938 subjects (19%) had diabetes. The overall 10-year survival for these diabetic patients was better following CABG (60%) than PTCA (46%). The survival advantage of surgery over angioplasty was greatest for patients treated with oral antidiabetic agents, less impressive for those on diet only, and nonexistent for those on insulin. The principal factors independently related to worse outcome in diabetic patients following PTCA were incomplete revascularization and sulfonylurea treatment. There are also indications that patients on sulfonylurea treatment during direct PTCA for myocardial infarction have higher in-hospital mortality than insulin- or diet-treated patients with diabetes.⁴⁴ The outcome of these registry-based reviews reinforces the conclusions of BARI according to which some subgroups of diabetic patients may derive particular benefit from CABG. PTCA in diabetic patients has also been associated with a very high rate of restenosis and a higher likelihood of procedure-related myocardial injury.⁴⁵

The purported risk of adverse cardiac effects with some sulfonylurea compounds is of particular interest in the context of revascularization, and the following explanations are offered to fuel the ongoing debate on this issue. In most species, the ATP-dependent potassium channels play an important role in ischemic preconditioning, which has a myocardial protective effect during ischemia followed by reperfusion. Traditional sulfonylureas such as glibenclamide act to stimulate insulin secretion by inhibiting the opening of the ATP-sensitive potassium channels in the pancreatic β cell. However, glibenclamide is not specific to the pancreas, but also influences ATP-dependent potassium channels in myocytes, mitochondria, and the vascular endothelium, thereby inactivating preconditioning. Inhibition of ATP-dependent potassium channels may also alter coronary vasorelaxation and diminish the decrease in myocardial contractile strength, impairing the protection of energy-depleted myocytes. Second-generation sulfonylureas such as glimepiride and gliclazide are considered more pancreas-specific, thus less liable to be active on

myocardial and vascular tissue.⁴⁶ However, this needs to be tested in large trials with clinical outcomes.

In light of the above, it may be speculated that CABG, through the more complete revascularization it affords, is less dependent on ischemic preconditioning than PTCA, in which ischemic preconditioning may play a more important role. Another speculation is that improved metabolic control, presumably with insulin, may improve the outcome of PTCA in diabetic patients, since many factors associated with insulin resistance and hyperglycemia are implicated in the process of restenosis. Furthermore, strict insulin-based metabolic control would probably decrease platelet aggregability and improve spontaneous fibrinolytic activity, two factors of importance in the process of restenosis, and possibly even more so in the promotion of acute ischemic complications following PTCA. Diabetics treated with GPIIb/IIIa-blocking agents have recently been shown to fare particularly well thanks to a reduction in postprocedural myocardial injury.

As emphasized in the introduction to this section, comparisons between PTCA and CABG in diabetic patients are limited by the fact that they are based on subgroup analysis or retrospectively collected registry data. Considering the large numbers of diabetic patients that undergo either PTCA or CABG, prospective randomized trials are needed and should be feasible. These should include the best available backup therapy and randomization to aggressive, rational insulin-based metabolic intervention or conventional antidiabetic treatment. There is a possibility that such treatment may considerably improve the outcome in PTCA and CABG, and decrease the currently reported difference in outcome between these two procedures.

MYOCARDIAL INFARCTION

Until recently, some treatments that may be particularly effective in diabetic patients have often been withheld. One example is thrombolysis, which, based on a single case report, was discouraged due to unverified worries about bleeding. Likewise, β -blockade has often been withheld on the strength of concerns about deterioration of metabolic control and blunting of the warning signals of hypoglycemia. These are typical examples of myths that may have cost lives. Although only partly based on prospective trials, there is firm evidence that aggressive treatment with β -blockers and metabolic intervention in fact improve prognosis in diabetic patients with acute myocardial infarction.



Thrombolysis and acetylsalicylic acid

Diabetic patients have a higher mortality following myocardial infarction than nondiabetic patients. A meta-analysis of 43 343 myocardial infarction patients, of whom 10% had a history of diabetes, showed that thrombolysis resulted in a considerable reduction in mortality in both groups, and that this reduction was more prominent in the diabetic group: the number of lives saved by thrombolytic therapy was 37 per 1000 treated patients in the diabetic cohort, compared with 15 per 1000 in those without diabetes mellitus.⁴⁷ Angiographic data indicate a similar patency rate in patients with and without diabetes mellitus after thrombolytic therapy. Due to the higher risk, the benefit-to-risk ratio of thrombolytic treatment is more favorable in diabetic than in nondiabetic patients. Extensive review of the literature does not reveal any increased propensity for hemorrhagic complications in subjects with diabetes mellitus who have been subjected to thrombolytic treatment.

Reduction in platelet aggregation by means of aspirin results in a substantial mortality and morbidity reduction in all patients with manifestations of CAD, including in the post-myocardial infarction phase.⁴⁸ It has been claimed that diabetic patients need large doses of aspirin for the suppression of platelet-derived thromboxane A₂. There is, however, no evidence that aspirin would be ineffective in diabetic patients. For the time being, and in the absence of further data, it is recommended that aspirin be used for the same indications and at the same dosage in diabetic patients as in those without diabetes.

ACE inhibitors

The only study that reports on the outcome of diabetic patients receiving ACE inhibitors early after myocardial infarction is Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI-3).⁴⁹ Fifteen percent of the study's 18 131 patients had diabetes mellitus. The decrease in 6-week mortality was significantly greater in diabetic than in nondiabetic patients receiving the ACE inhibitor lisinopril, whereas this decrease was not statistically significant in the nondiabetic group. The explanation may be that patients with diabetes are at increased risk of heart failure following acute myocardial infarction. Several studies have indicated that ACE inhibition is most effective in patients with compromised left ventricular function. This finding should encourage more widespread use of ACE inhibitors in diabetic postinfarction patients.

β-Blockers

β-Blockers decrease postinfarction mortality and new infarcts in patients with a history of diabetes mellitus. In the Gothenburg metoprolol trial, this decrease was much more marked in the diabetic subgroup than among nondiabetic patients (*Figure 1*).⁵⁰ This finding was confirmed in similarly defined patients such as in the Norwegian timolol study⁵¹ and the Beta-blocker Heart Attack Trial.⁵²

There are several possible explanations for the particularly favorable effect of β-blockers during and after myocardial infarction in diabetic patients. β-Blockers have been shown to redirect myocardial metabolism toward glucose utilization, decreasing free fatty acid utilization. This shift reduces myocardial oxygen consumption and may contribute to myocardial tissue preservation. β-Blockade may also improve diabetic autonomic dysfunction through a decrease in vagal tone and an increase in sympathetic tone. Several studies have reported that diabetic patients have a higher admission heart rate than nondiabetic patients. This tachycardia is reduced by β-blockade, thus protecting the myocardium at risk. Furthermore, diabetics are at increased risk of heart failure, and recent trials⁵³ have clearly documented the beneficial effects of β-blockade in heart failure patients.

To conclude, liberal use of β-blockade is advocated in diabetic patients with CAD, even though its rationale is based on subgroup analysis. The fact that the beneficial effects that have been reported in available studies have a solid pathophysiological basis lends further support to this view.

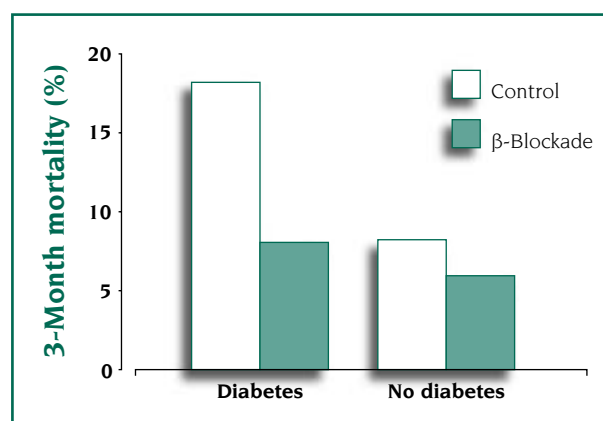


Figure 1. Three-month mortality in diabetic and nondiabetic patients treated with the β-blocker metoprolol in connection with myocardial infarction in the Gothenburg metoprolol trial. Total number of patients = 1395, diabetic patients = 120 (9%). Based on data from ref 50.

Metabolic intervention

Metabolic control is of major importance during acute myocardial infarction, since, in diabetic patients, fatty acid metabolism is increased and glycolysis compromised, impairing both ischemic and non-ischemic myocardial tissues. One way to decrease free fatty acid oxidation is by infusing insulin and glucose. Continuous intensive insulin treatment may also improve platelet function, correct the disturbed lipoprotein pattern, and decrease plasminogen activator inhibitor (PAI-1) activity, thereby improving spontaneous fibrinolysis. All these factors are closely interrelated and may play a major role in the increased mortality and morbidity following myocardial infarction in diabetic patients.

These concepts are supported by the findings from the Swedish DIGAMI study (Diabetic patients receiving Insulin-Glucose infusion during Acute Myocardial Infarction).^{54,55} In DIGAMI, 620 patients with diabetes

and acute myocardial infarction were randomly assigned to a control group or a group receiving intensive insulin treatment initiated by insulin-glucose infusion during the first 24 hours following a myocardial infarction. The 1-year mortality rate was reduced by 30% in the intensively treated group, and therapy tended to favorably influence all cardiovascular causes of death. Long-term follow-up of between 1.6 and 5.6 years (mean 3.4) showed an 11% absolute mortality reduction in the group subjected to intensive insulin treatment, amounting to 1 saved life for every 9 patients treated (Figure 2A). Of particular interest is the fact that patients without previous insulin and at relatively low risk benefited the most (Figure 2B). The average decrease in HbA_{1c} (used as an index of improved metabolic control) in these patients was 1.4%. Multivariate analysis showed that old age, previous heart failure, diabetes duration, admission blood glucose, and admission HbA_{1c} were independent predictors of mortality in the total DIGAMI cohort. Parameters such as previous myocardial infarction, hypertension,

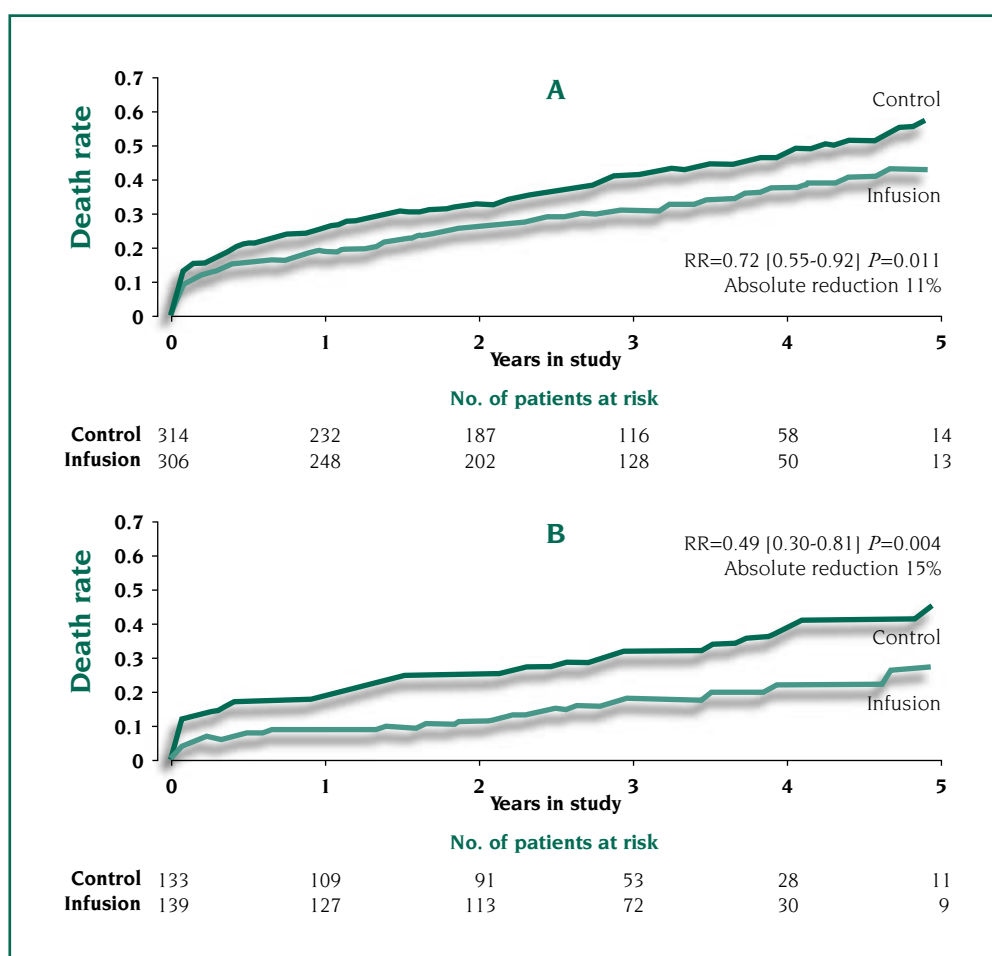


Figure 2. A: Actuarial mortality curves during long-term follow-up (mean 3.4 years) in patients receiving insulin-glucose infusion and in a control group among the total DIGAMI study cohort. Death rate is No. of deaths / No. originally in group. Total number of patients = 620.

B: Actuarial mortality curves during long-term follow-up (mean 3.4 years) in patients receiving insulin-glucose infusion and in a control group of patients at low risk who were not taking insulin before randomization among the total DIGAMI study cohort. Death rate is No. of deaths / No. originally in group. Total number of patients = 272.

Adapted from ref 55: Malmberg K, for the DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. Prospective randomized study of intensive insulin treatment on long-term survival after acute myocardial infarction in patients with diabetes mellitus. *BMJ*. 1997;314:1512-1515. Copyright © 1997, British Medical Association.

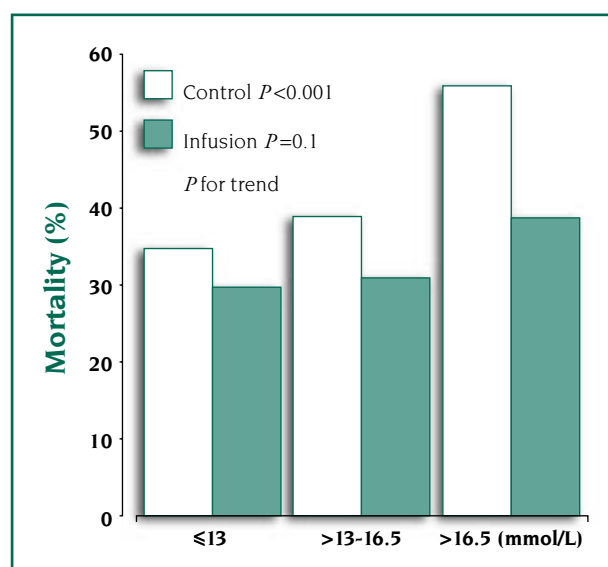


Figure 3. Long-term mortality (mean, 3.4 years; range, 1.6-5.6 years) according to admission blood glucose tertiles in the DIGAMI study.

Adapted from ref 56: Malmberg K, Norhammar A, Wedel H, Rydén L. Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction. Long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) Study. *Circulation*. 1999;99:2626-2632. Copyright © 1999, American Heart Association, Inc.

smoking, or female gender did not have independent predictive value. An interesting finding was that the well-established relationship between admission glucose and mortality was seen only among the control patients, suggesting that appropriate metabolic treatment during the peri-infarction period could attenuate the harmful effect of a high admission glucose (Figure 3).⁵⁶ The findings also indicated that β -blockers improved survival more in control subjects, whereas thrombolysis was most efficient in the insulin group. Thus, age, previous myocardial damage, and, not least, the current state of glucose metabolism, were predictive of long-term outcome in diabetic patients with myocardial infarction. Institution of intensive insulin treatment reduced the risk considerably, while β -blockers also demonstrated striking secondary preventive effects.

The results of the DIGAMI study were lent further credence by a recent meta-analysis⁵⁷ and the ECLA (Estudios Cardiológicos Latino America) glucose-insulin-potassium (GIK) pilot trial,⁵⁸ while a Polish study seemed to strike a discordant note.⁵⁹

- The meta-analysis,⁵⁷ which included a total of 1932 predominantly nondiabetic patients, showed a proportional mortality reduction of 28%, and an absolute

number of lives saved of 49 per 1000 patients treated with GIK. The treatment effect was even more manifest when only studies utilizing high-dose intravenous GIK regimens were taken into consideration. The effect of GIK treatment might be even more dramatic in the field of reperfusion, since experimental studies have estimated that GIK treatment before reperfusion has the potential to protect ischemic myocardium for 10 hours or more.

- The ECLA trial,⁵⁸ which included 400 patients, showed a nonsignificant trend toward reduction in major and minor in-hospital events in patients allocated to GIK. However, among the 252 patients who underwent reperfusion therapy, there was a significant (66%) reduction in mortality and a consistent trend toward fewer in-hospital events in the GIK group compared with controls.

- In contrast, a recent study from Poland⁵⁹ reported that there was actually an increase in mortality with the use of GIK. However, the Polish study used a lower dose of glucose and insulin and targeted a low-risk population, which may explain the discordant results.

To conclude, this evidence in favor of GIK therapy prompted a recent editorial in *The Lancet*,⁶⁰ which stated that “these data are so convincing that diabetic patients with acute myocardial infarction should be given a modified regimen in accordance with the DIGAMI protocol.”

CONGESTIVE HEART FAILURE

The treatment of symptomatic CHF is currently based on principles such as those outlined in the ESC guidelines,⁶¹ as discussed below.

Diuretics

Diuretics are mandatory in symptomatic patients, but whether their use improves or worsens the prognosis is not known. Although no studies have specifically looked into the outcome of the use of diuretics in a diabetic heart failure population, loop diuretics are recommended rather than diuretics that risk further impairing the glucose metabolic state.

ACE inhibitors

Subgroup analysis of mortality from large clinical trials of ACE inhibitors in heart failure reveals that mortality, as might be expected, is higher in the diabetic cohort than in nondiabetic patients.

- In the prevention arm of SOLVD,⁶² the efficacy of the ACE inhibitor enalapril was found to be somewhat more marked in diabetic than nondiabetic patients, while it was approximately similar in the treatment arm of SOLVD.⁸
- The Assessment of Treatment with Lisinopril And Survival (ATLAS) trial⁶³ compared high and low doses of the ACE inhibitor lisinopril over a period of 45 months in heart failure patients of New York Heart Association (NYHA) classes II-IV. Out of the total patient cohort of 3164 patients, 611 were diabetics. Mortality was considerably higher in the diabetic subgroup than in the nondiabetics. When compared with the respective low-dose lisinopril groups, nondiabetic patients in the high-dose lisinopril group had a 6% lower risk of death, whereas diabetic patients in the high-dose lisinopril group had a 14% lower risk of death. This emphasizes the need for appropriate doses of ACE inhibitors for diabetic as well as nondiabetic patients.⁶⁴
- Post-myocardial infarction patients with compromised left ventricular function (left ventricular ejection fraction [LVEF] <40%) were assessed in the Survival And Ventricular Enlargement (SAVE) study.⁶⁵ The diabetic cohort had a higher morbidity and total mortality than the nondiabetic group. In the diabetic patients, treatment with the ACE inhibitor captopril improved this unfavorable outcome to an extent similar to that in nondiabetic patients.

In conclusion, ACE inhibitors are of value in diabetic patients with CHF. Perhaps the relative efficacy is more apparent in this subgroup than in nondiabetic patients, in keeping with the fact that patients at high risk benefit the most.

β-Blockers

No studies specifically address the use of β-blockers in diabetic patients with heart failure except for a small subgroup analysis from one of the branches of the American carvedilol program,⁶⁶ which indicated an even larger treatment effect in patients with diabetes. Findings from this analysis and experience gained from treating acute myocardial infarction and post-myocardial infarction patients suggest that β-blockers are of benefit in diabetics with CHF.

Metabolic intervention

There are several reasons to assume that the prognosis of patients with concomitant heart failure and diabetes

mellitus would improve with strict metabolic control. Thus, the suggested harmful effect of increased free fatty acid oxidation and decreased glucose utilization could be attenuated by such treatment. Metabolic intervention with dichloroacetate has been used in nondiabetic patients with severe heart failure.⁶⁷ This compound stimulates pyruvate dehydrogenase activity, thereby facilitating glucose oxidation, while inhibiting free fatty acid metabolism. Dichloroacetate resulted in an increase in myocardial lactate extraction, together with an increase in forward stroke volume and left ventricular minute work, and a concomitant decrease in myocardial oxygen consumption. It would be of considerable interest to test such treatments in diabetic populations with heart failure. Also of interest would be to study whether improved metabolism favorably influences the efficacy of conventional therapy in diabetic patients with heart failure and has preventive value regarding the development of heart failure in diabetic subjects with cardiac disease. Studies on the impact of strict metabolic control in patients with congestive heart failure are urgently needed.

CONCLUDING REMARKS

This review attempted to summarize the available information on diabetic patients with cardiovascular disease. It is evident that few studies have addressed this topic using a prospective trial design in diabetic patients only, or with prestratification of diabetic patients according to a strictly defined diagnosis and treatment. Data from the only study conducted specifically in diabetic patients, DIGAMI,^{54,55} strongly favor the concept of strict metabolic control based on insulin, at least in diabetic patients with myocardial infarction. There are several reasons to believe that such improved metabolic intervention would make sense in several other manifestations of cardiovascular disease in diabetic subjects. Improved knowledge among diabetologists about the treatment and prevention of cardiovascular complications, and among cardiologists about diabetology, is a prerequisite for progress in the care of patients with diabetes mellitus and cardiovascular disease. In view of the large and rapidly increasing number of patients at risk, it is certainly urgent to get started. The high costs associated with the management of diabetic patients with cardiovascular disease suggest that improved therapy will very likely be cost-effective, as, for example, proved to be the case with the aggressive metabolic intervention implemented in diabetic patients with myocardial infarction in the DIGAMI study.



THREE KEY QUESTIONS

Having established that ensuring stricter metabolic control is of paramount importance in reducing the diabetic heart's vulnerability to cardiovascular disease, it is now time to turn to the subtler aspects of the management of specific cardiovascular complications in the diabetic patient, which we could only touch upon here. This task now falls to the experts who will address three major topics. In "**What is the most effective management of hypertension in diabetes?**" Lionel Opie looks at the implications of the forecast increase in the number of diabetic patients developing hypertension; in "**What is the most effective management of heart failure in diabetic patients?**" Aldo Maggioni and Giulio Zuanetti give their view on how to deal with what they believe is by far the most important complication of diabetes; finally, in "**How can coronary artery disease and infarction be best managed in diabetes?**" Laura Benzaquen and Richard Nesto take stock of the increased propensity of diabetic patients, compared with their nondiabetic counterparts, to suffer acute coronary events, and give a roundup of the means at our disposal for both the acute and long-term management of diabetic patients with CAD.

REFERENCES

- 1. Gu K, Cowie CC, Harris MI.**
Diabetes and decline in heart disease mortality in US adults.
JAMA. 1999;281:1291-1297.

- 2. UK Prospective Diabetes Study Group.**
Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39.
BMJ. 1998;317:713-720.

- 3. King H, Aubert RE, Herman WH.**
Global burden of diabetes 1995-2025. Prevalence, numerical estimates and projections.
Diabetes Care. 1998;21:1414-1431.

- 4. Clark CM, Perry RC.**
Type 2 diabetes and macrovascular disease. Epidemiology and etiology.
Am Heart J. 1999;138:330-333.

- 5. Kannel WB, McGee DL.**
Diabetes and cardiovascular disease. The Framingham study.
JAMA. 1979;214:2035-2038.

- 6. Andersson B, Waagstein F.**
Spectrum and outcome of congestive heart failure in a hospitalised population.
Am Heart J. 1993;126:632-640.

- 7. The CONSENSUS Trial Study Group**
Effect of enalapril on mortality in severe congestive heart failure.
N Engl J Med. 1987;316:1429-1435.

- 8. The SOLVD Investigators.**
Effect of enalapril on survival in patients with reduced left ventricular ejection fraction and congestive heart failure.
N Engl J Med. 1991;325:293-302.

- 9. Suskin N, McKelvie RS, Rouleau J, Sigouin C, Wiecek E, Yusuf S.**
Increased insulin and glucose levels in heart failure.
J Am Coll Cardiol. 1998;31(suppl A):249A.

- 10. Reis SE, Holubkov R, Edmundowicz D, et al.**
Treatment of patients admitted to hospital with congestive heart failure: speciality-related discrepancies in practice patterns and outcomes.
J Am Coll Cardiol. 1997;30:733-738.

- 11. Amato L, Paolisso G, Cacciatore F, et al, on behalf of the Osservatorio Geriatrico Regione Campania Group.**
Congestive heart failure predicts the development of non-insulin-dependent diabetes mellitus in the elderly.
Diabetes Metab. 1997;23:213-218.

12. Chae CU, Glynn RJ, Manson JE, Guralnik JM, Taylor JO, Pfeffer MA.

Diabetes predicts congestive heart failure risk in the elderly.
Circulation. 1998;98(suppl 1):721.

13. Lundbäck K.

Diabetic angiopathy: a specific vascular disease.
Lancet. 1954;2:377-379.

14. Hardin N.

The myocardial and vascular pathology of diabetic cardiomyopathy.
Cor Art Dis. 1996;7:99-108.

15. Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S.

Effect of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial.
Lancet. 1998;351:1755-1762.

16. Woodfield SL, Lundergran CF, Reiner JS, et al.

Angiographic findings and outcome in diabetic patients treated with thrombolytic therapy for acute myocardial infarction: the GUSTO-I experience.
J Am Coll Cardiol. 1996;28:1661-1669.

17. Stone P, Muller J, Hartwell T, et al, and the MILIS study group.

The effect of diabetes mellitus on prognosis and serial left ventricular function after acute myocardial infarction: contribution of both coronary disease and diastolic left ventricular dysfunction to the adverse prognosis.
J Am Coll Cardiol. 1989;14:49-57.

18. Nesto RW, Phillips RT, Kett KG, Hill T, Young E, Leland S.

Angina and exertional myocardial ischemia in diabetic and nondiabetic patients: assessment by exercise thallium scintigraphy.
Ann Int Med. 1988;108:170-175.

19. Fisher BM, Frier BM.

Evidence for a specific heart disease of diabetes in humans.
Diabetic Med. 1990;7:478-484.

20. Youkoyama I, Momomura SI, Ohtake T, et al.

Reduced myocardial flow reserve in non-insulin-dependent diabetes mellitus.
J Am Coll Cardiol. 1997;30:1472-1477.

21. Rodrigues B, Cam MC, McNeill JH.

Metabolic disturbances in diabetic cardiomyopathy.
Mol Cell Biol Biochem. 1998;180:53-57.

22. Niakan E, Harati Y, Rolak LA, Comstock JP, Rokey R.

Silent myocardial infarction and diabetic cardiovascular autonomic neuropathy.
Arch Intern Med. 1986;146:2229-2230.

23. Ewing D.

Cardiac autonomic neuropathy.
In: Jarret R, ed. *Diabetes and Heart Disease.* Amsterdam, The Netherlands: Elsevier; 1984:99-132.

24. Kwaan H.

Changes in blood coagulation, platelet function and the plasminogen-plasmin system in diabetes.
Diabetes. 1992;41:32-35.

25. Lincoff AM, Califf RM, Moliterno DJ, et al.

Complementary clinical benefits of coronary-artery stenting and blockade of platelet glycoprotein IIb/IIIa receptors.
N Engl J Med. 1999;341:319-327.

26. McGill JB, Schneider DJ, Arfken CL, Sobel BE.

Factors responsible for impaired fibrinolysis in obese subjects and NIDDM patients.
Diabetes. 1994;43:104-109.

27. Malmberg K, Rydén L, Wedel H.

Calcium antagonists, appropriate therapy for diabetic patients with hypertension?
Eur Heart J. 1998;19:1269-1272.

28. Curb JD, Pressel SL, Cutler JA, et al, For the Systolic in Elderly Program Cooperative Research Group.

Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension.
JAMA. 1996;276:1886-1892.

29. Tuomilehto J, Rastenyte D, Birkenhäger W, et al.

Effects of calcium channel blockade in older patients with diabetes and systolic hypertension.
N Engl J Med. 1999;340:677-684.

30. UK Prospective Diabetes Study Group.

Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes. UKPDS 39.
BMJ. 1998;317:713-720.

31. Hansson L, Lindholm LH, Niskanen K, et al, for the Captopril Prevention Project (CAPPP) Study Group.

Effect of angiotensin-converting enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP).
Lancet. 1999;353:611-616.

32. 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.
N Engl J Med. 1998;338:645-652.

**33. Tatti P, Pahor M, Byington RP, et al.**

Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM.

Diabetes Care. 1998;21:597-603.

34. Turner RC, Millns H, Neil HA, et al.

Risk factors for coronary artery disease in non-insulin-dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS 23).

BMJ. 1998;316:823-828.

35. American Diabetes Association.

Management of dyslipidemia in adults with diabetes.

Diabetes Care. 1998;22:179-182.

36. Task Force Report.

Prevention of coronary heart disease in clinical practice.

Eur Heart J. 1998;19:1434-1503.

37. Downs JR, Clearfield M, Weis S, et al.

Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AF/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study.

JAMA. 1998;279:1615-1622.

38. Koskinen P, Manttari M, Manninen V, Huttunen JK, Heinonen OP, Frick MH.

Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study.

Diabetes Care. 1992;15:820-825.

39. Pyörälä K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G.

Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S).

Diabetes Care. 1997;20:614-620.

40. Goldberg RB, Mellies MJ, Sacks FM, et al.

Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the cholesterol and recurrent events (CARE) trial. The CARE Investigators.

Circulation. 1998;98:2513-2519.

41. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group.

Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels.

N Engl J Med. 1998;339:1349-1357.

42. BARI Investigators.

Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multi-vessel disease: the Bypass Angioplasty Revascularisation Investigation (BARI).

Circulation. 1997;96:1761-1769.

43. Keefe JH, Blackstone EH, Sergeant P, McCallister BD.

The optimal role of coronary revascularization for diabetics. A risk-adjusted long-term study comparing coronary angioplasty and coronary bypass surgery.

Eur Heart J. 1998;19:1696-1703.

44. Garratt KN, Brady PA, Hassinger NL, Grill DE, Terzic A, Holmes D.

Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction.

J Am Coll Cardiol. 1999;33:119-124.

45. Aronson D, Bloomgarden Z, Rayfield EJ.

Potential mechanisms promoting restenosis.

J Am Coll Cardiol. 1996;27:528-535.

46. Wikström G, Malmberg K, Rydén L.

Improved knowledge of antidiabetic treatment—a necessity for the modern cardiologist.

Eur Heart J. 1999;20:403-405.

47. Fibrinolytic Therapy Trialists (FTT) Collaborative Study Group.

Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1000 patients.

Lancet. 1994;343:311-322.

48. No authors listed.

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. Antiplatelet Trialists Collaboration [Published erratum appears in *BMJ* 1994;308:1540].

BMJ. 1994;308:81-108.

49. Zuanetti G, Latini R, Maggioni A, Franzosi M, Santoro L, Tognioni G.

Effect of the ACE-inhibitor lisinopril on mortality in diabetic patients with acute myocardial infarction: data from the GISSI-3 study.

Circulation. 1997;96:4239-4245.

50. Malmberg K, Herlitz J, Hjalmarsen A, Rydén L.

Effects of metoprolol on mortality and late infarction in diabetics with suspected acute myocardial infarction. Retrospective data from two large-scale studies.

Eur Heart J. 1989;10:423-428.

51. Gundersen T, Kjekshus J.

Timolol treatment after myocardial infarction in diabetic patients.
Diabetes Care. 1983;6:285-290.

52. No authors listed.

A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results.
JAMA. 1982;26:1707-1714.

53. No authors listed.

Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF).
Lancet. 1999;353:2001-2007.

54. Malmberg K, Rydén L, Efendic S, et al.

A randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction: effects on one-year mortality.
J Am Coll Cardiol. 1995;26:57-65.

55. Malmberg K, for the DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group.

Prospective randomized study of intensive insulin treatment on long-term survival after acute myocardial infarction in patients with diabetes mellitus.
BMJ. 1997;314:1512-1515.

56. Malmberg K, Norhammar A, Wedel H, Rydén L.

Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction. Long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) Study.
Circulation. 1999;99:2626-2632.

57. Fath-Ordoubadi F, Beatt KJ.

Glucose-insulin-potassium therapy for treatment of acute myocardial infarction: an overview of randomized placebo-controlled trials.
Circulation. 1997;96:1152-1156.

58. Diaz E, Romero G, on behalf of the ECLA collaborative group.

Metabolic modulation of acute myocardial infarction. The ECLA glucose-insulin-potassium trial.
Circulation. 1998;98:2227-2234.

59. Ceremuzynski L, Budaj A, Czepiel A, Achremczyk P, Smielak-Korombel W, Maciejewicz J, on behalf of the Pol-GIK Study Investigators.

Low-dose polarizing mixture (glucose-insulin-kalium) in acute myocardial infarction. Randomized multicentre Pol-GIK study.
Eur Heart J. 1997;18(suppl):167. Abstract P1054.

60. Opie LH.

Proof that glucose-insulin-potassium provides metabolic protection of ischaemic myocardium.
Lancet. 1999;353:768-769.

61. The Task Force of the European Society of Cardiology.
Guidelines for the treatment of heart failure.

Eur Heart J. 1997;18:736-753.

62. The SOLVD Investigators.

Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions.
N Engl J Med. 1992;327:685-691.

63. Packer M, Poole-Wilson PA, Armstrong PW, et al.

Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group.
Circulation. 1999;100:2312-2318.

64. Soläng L, Malmberg K, Rydén L.

Diabetes mellitus and congestive heart failure. Future knowledge needed.
Eur Heart J. 1999;20:789-795.

65. Moye LA, Pfeffer MA, Wun CC, et al.

Uniformity of captopril benefit in the SAVE study: subgroup analysis. Survival And Ventricular Enlargement study.
Eur Heart J. 1994;15(suppl B):2-8.

66. Bristow M, Gilbert EM, Abraham WT, et al.

Effect of carvedilol on left ventricular function and mortality in diabetic versus non-diabetic patients with ischemic or non-ischemic dilated cardiomyopathy.
Circulation. 1996;94(suppl A):I664.

67. Bersin RM, Wolfe C, Kwasman M, et al.

Improved haemodynamic function and mechanical efficiency in congestive heart failure with sodium dichloroacetate.
J Am Coll Cardiol. 1994;23:1617-1624.
