# Diabetes and the Heart

# Editorial

*As* **Dialogues in Cardiovascular Medicine** *enters its fifth year and the new millennium, we would like to share some exciting news and additions to the journal. We are delighted to inform our readers that* **Dialogues** *has been officially approved by the Board of the European Society of Cardiology as part of its continuing education program, and a subscription to* **Dialogues** *will now be provided to every Fellow of the ESC. This Fellowship benefit has been made possible by an unrestricted educational grant from the Servier Research Group, and the Editors and the ESC are very grateful for this support. This issue of* **Dialogues** *is devoted to "Diabetes and the Heart," and we are particularly indebted to Professor Lars Rydén, the President of the ESC, for contributing to this issue.*

*This year we will be introducing a number of new features to* **Dialogues**, *which will take the form of a series of short articles grouped under the* ***Fascinoma Cardiologica*** *heading, each being identified by a distinctive icon. "Trails of Discovery" will describe some of the fascinating background to the development of major drug groups; "Icons of Cardiology" will provide a personal overview of some of the great historical figures in the cardiovascular world; "Plants in Cardiology" will show the enormous impact that naturally occurring compounds have had in the identification and development of many cardiovascular drugs; "A Lexicon of the Heart" will give definitions and descriptions for some of the buzzwords that have crept into the vocabulary of cardiology; and, finally, "Surfing the Heart" will link our readers to the hottest cardiovascular web sites. These articles will be authored by guest writers including Arnold Katz, Claudio Ceconi, Anirban Banerjee, Desmond Fitzgerald, and Robert Jennings.*

***Roberto Ferrari and David J. Hearse***
***Editors in Chief***

# 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 ≤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 al[1] clearly shows that patients with diabetes mellitus have not benefited from this to the same extent as their non-diabetic 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** | CAPtropril 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 Cardiologicos 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 survey[4] 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 study[5] 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 al[10] 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 data[11] 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 patients[12] 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 Hardin[14] 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 studies[18] 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 studies[19] 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 al[21] 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 $\alpha_1$-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 $A_2$ 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 observations[25] 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–1[26] 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 diabetic 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 (CAPPP) study[31] 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 (%) primary outcome no DM | Risk reduction (%) primary outcome DM | Risk reduction (%) combined end point† no DM | Risk reduction (%) combined end point† DM | Meta-analyses risk reduction (%) combined end point† no DM | Meta-analyses 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 glycated 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 subgoup analyses of clinical trials. The American Diabetes Association[35] 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 study[38] 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) trial[41] 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 study[43] 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 $A_2$. 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 study[51] 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 trials[53] 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.

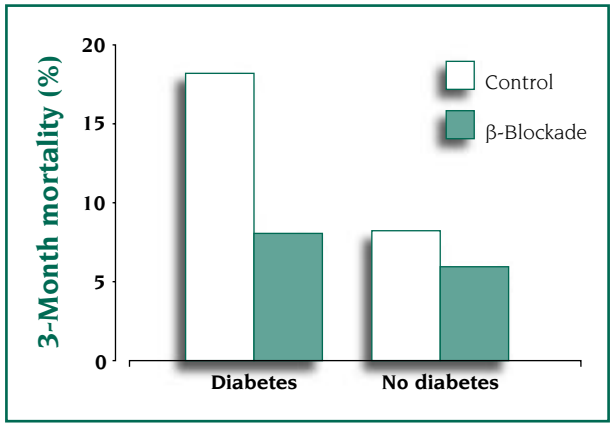


***Figure 1.*** *Three-month mortality in diabetic and nondiabetic patients treated with the β-blocker metoprolol in connection with myocardial infarction in the Gothenburg metoprolol trial. Total number of patients = 1395, diabetic patients = 120 (9%). Based on data from ref 50.*

## 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,

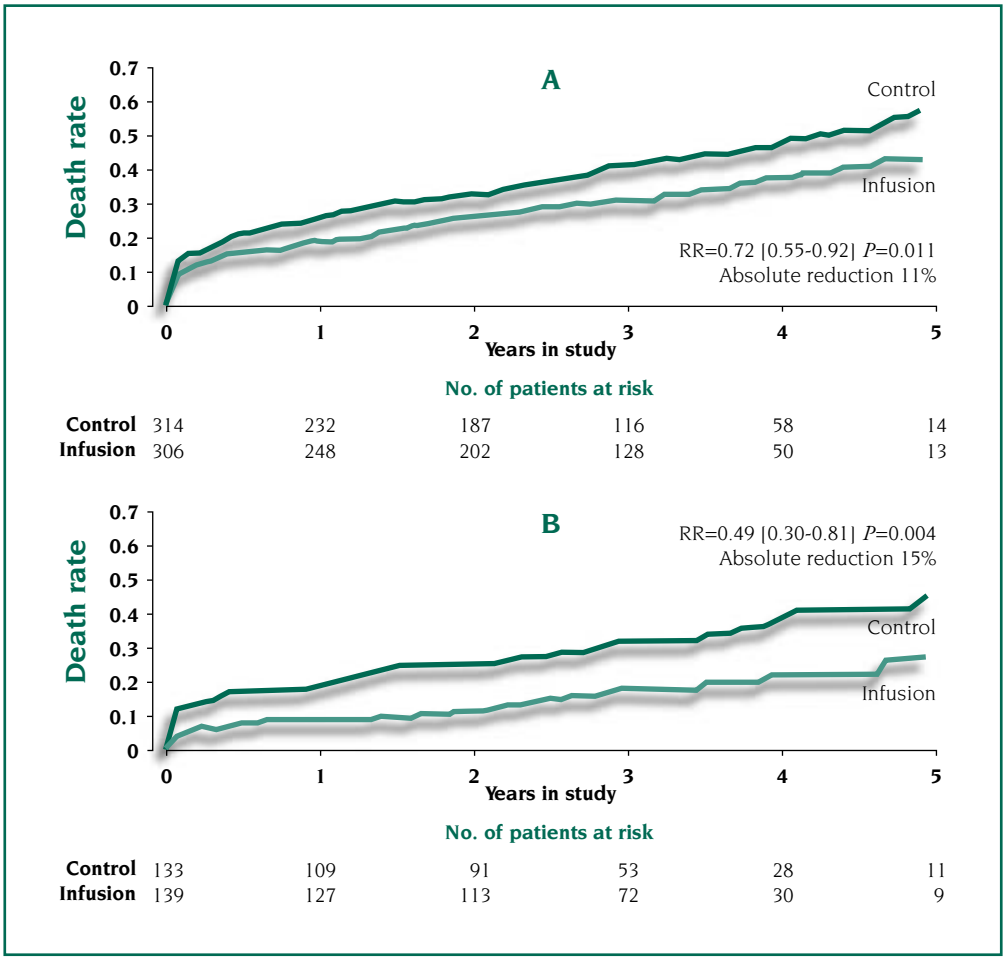


***Figure 2.** A: Actuarial mortality curves during long-term follow-up (mean 3.4 years) in patients receiving insulin-glucose infusion and in a control group among the total DIGAMI study cohort. Death rate is No. of deaths / No. originally in group. Total number of patients = 620.*

*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.*

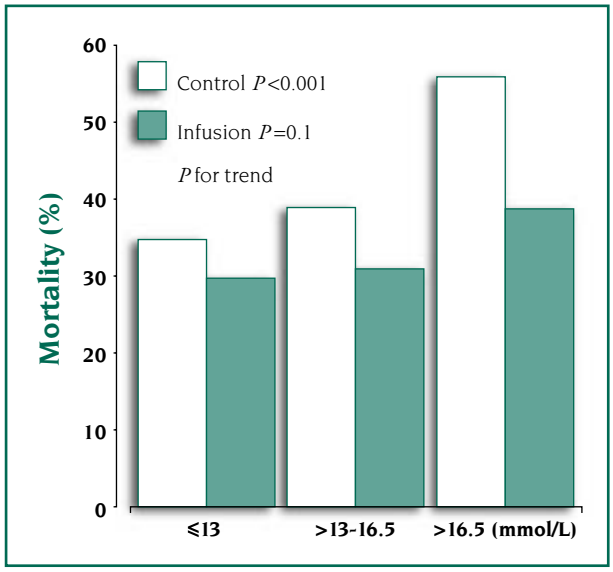


***Figure 3.*** *Long-term mortality (mean, 3.4 years; range, 1.6-5.6 years) according to admission blood glucose tertiles in the DIGAMI study.*

*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-analysis[57] and the ECLA (Estudios Cardiologicos 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 Poland[59] 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) trial[63] 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. Kanel 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 I):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 on 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 randomised trial comparing CABG and PTCA in patients with multivessel 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, Hjalmarsson 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;84(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.

# Diabetes and the Heart

*Expert Answers to Three Key Questions*

1

## What is the most effective management of hypertension in diabetes?

***L.H. Opie***

2

## What is the most effective management of heart failure in diabetic patients?

***A.P. Maggioni, G. Zuanetti***

3

## How can coronary artery disease and infarction be best managed in diabetes?

***L.R. Benzaquen, R.W. Nesto***

# What is the most effective management of hypertension in diabetes?

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*Over half of type 2 diabetics, particularly women, are likely to be hypertensive at age 50 using the recently recommended cutoff of 130/85 mm Hg. The cause is multifactorial and includes insulin resistance, which is closely related to obesity, itself a risk factor for hypertension. The first-line treatment is lifestyle modification (exercise, weight loss, and smoking withdrawal). This must almost always be aided by drugs, preferably a long-acting angiotensin-converting enzyme inhibitor on the grounds of hard end points (cardiovascular events), renoprotection, and quality of life (decreased impotence), often combined with a low-dose diuretic or a dihydropyridine calcium channel blocker. Proteinuria warrants even more stringent blood pressure control (125/75 mm Hg). Finally, aggressive use of statins may be beneficial even if initial cholesterol levels are only average.*

**Keywords:** hypertension; diabetes; insulin resistance; nephropathy; lifestyle; ACE inhibitor; diuretic; β-blocker; calcium channel blocker

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The new message, from three large studies, is that vigorous treatment of hypertension in diabetics can markedly reduce hard end points.[1-3] This means that more and more cardiologists and physicians treating hypertension will be seeing diabetic patients. The presence of diabetes profoundly increases the cardiovascular risk, largely through the adverse combination of diabetes and hypertension. Thus, the prediction charts of the British Joint Committees and several other bodies, such as the combined European Societies of Cardiology, Hypertension, and Atherosclerosis, are divided into those who have diabetes and those who do not. But, what is diabetes and what is hypertension? And is the type of diabetes of importance? As most diabetics presenting with hypertension will be type 2 (maturity-onset, non–insulin-dependent), this article will concentrate on this group.

## DIABETES MELLITUS AND HYPERTENSION: DEFINITIONS

### Diabetes mellitus and impaired fasting glucose

Recently, the diagnosis of diabetes has been simplified. In the USA, the new guidelines take a consistently elevated fasting blood glucose of 110 up to 125 mg/dL (6.1 to 6.9 mmol/L) as an impaired fasting glucose, and higher values as diabetes mellitus.[4] Elsewhere, the new proposals of the World Health Organization expert com-

**SELECTED ABBREVIATIONS AND ACRONYMS**

| | |
|---|---|
| **ACE** | angiotensin-converting enzyme |
| **DHP** | dihydropyridine |
| **EUCLID** | EURODIAB Controlled trial of Lisinopril in Insulin-dependent Diabetes |
| **HOPE** | Heart Outcomes Prevention Evaluation study |
| **HOT** | Hypertension Optimal Treatment study |
| **IFG** | impaired fasting glycemia |
| **IGT** | impaired glucose tolerance |
| **SHEP** | Systolic Hypertension in the Elderly Program |
| **SYST-EUR** | SYSTolic hypertension in elderly in EURope trial |
| **UKPDS** | United Kingdom Prospective Diabetes Study |

mittee[5] will probably be followed, diagnosing diabetes as a fasting plasma glucose of 7 mmol/L or more, with values of 6.1 mmol/L, but, below 7.0 mmol/L, representing impaired fasting glycemia (IFG). If the 2-hour glucose is also abnormal in a glucose tolerance test, being above 11.1 mmol/L, then there is impaired glucose tolerance (IGT). However, the major aim is simplification, and the new reliance is on the fasting glucose values, rather than on the glucose tolerance curve, which becomes less important than before.

### Definitions of hypertension

A sustained blood pressure (BP) value of 140/90 mm Hg or above is taken as hypertension by both the American and the international bodies.[6,7] For diabetics, both recommend that BP be reduced to 130/85 mm Hg or below. This means that any higher pressures are too high and, by definition, indicate hypertension. In reality, trial data show that a diastolic value of 82 mm Hg reduces hard end points,[1] but trial data to support the very low systolic recommendation are not yet available.

### Incidence of hypertension in diabetics

Taking the now outdated criteria for hypertension, ie, a BP equal to or exceeding 160/90 mm Hg, 35% of male and 46% of females with type 2 diabetes are hypertensive at a mean age of 52 years.[8] The incidence with the new lower criteria must therefore be even higher, probably exceeding 50%. Of interest, the higher incidence in females, though related to greater obesity, persists even when corrected for obesity.[8] As in nondiabetics, hypertension is a risk factor for coronary artery disease.

## MECHANISMS FOR HYPERTENSION IN DIABETICS

The origin of the hypertension frequently found in diabetics is probably multifactorial. In the more common type 2 diabetes, causes of hypertension may include obesity, insulin resistance, sodium retention, occult renal impairment, increased peripheral vascular resistance, and endothelial dysfunction *(Figure 1)*. The latter may, hypothetically, participate in a vicious circle mechanism. Insulin resistance may precede the development of overt type 2 diabetes by more than a decade.[9] Probably, much or all of the insulin resistance is closely related to obesity, itself a risk factor for hypertension.[8] The mechanisms for obesity-related hypertension include increased cardiac output and adrenergic activity. The metabolic cardiovascular syndrome describes the association of central obesity, hypertension, and type 2 diabetes and atherosclerotic cardiovascular disease, in which a key role is played by insulin resistance *(Figure 2)*.

### Insulin resistance

The basic pathophysiology of the two types of diabetes differs: type 1 diabetes is straightforward insulin deficiency, while type 2 diabetes is associated with hyperinsulinemia and insulin resistance.
Insulin resistance has multiple mechanisms of action, including failure to decrease circulating free fatty acid levels to normal values.[10] Free fatty acids may in turn promote vasoconstrictor $\alpha_1$-adrenergic activity, at least in normal volunteers. Additionally, insulin resistance reduces skeletal muscle blood flow.

### Antihypertensive drugs

Antihypertensive drugs further impair insulin resistance. A mixture of β-blockade, diuretics, and hydralazine, in variable amounts and over 9 years, precipitated diabetes in some subjects who already had

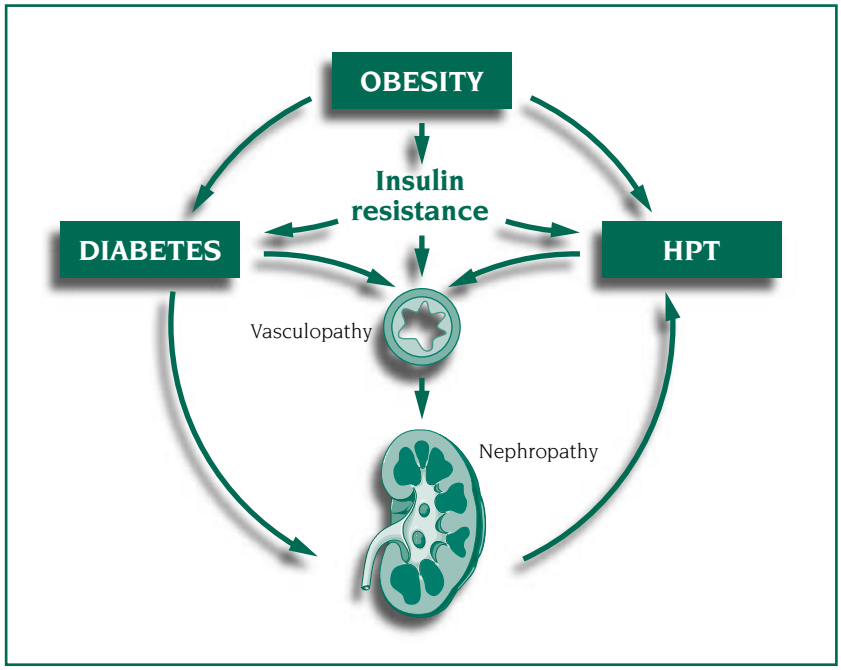


***Figure 1.*** *Complex links between diabetes mellitus, hypertension, insulin resistance, and nephropathy. HPT, hypertension. Copyright © L.H. Opie, 1999.*

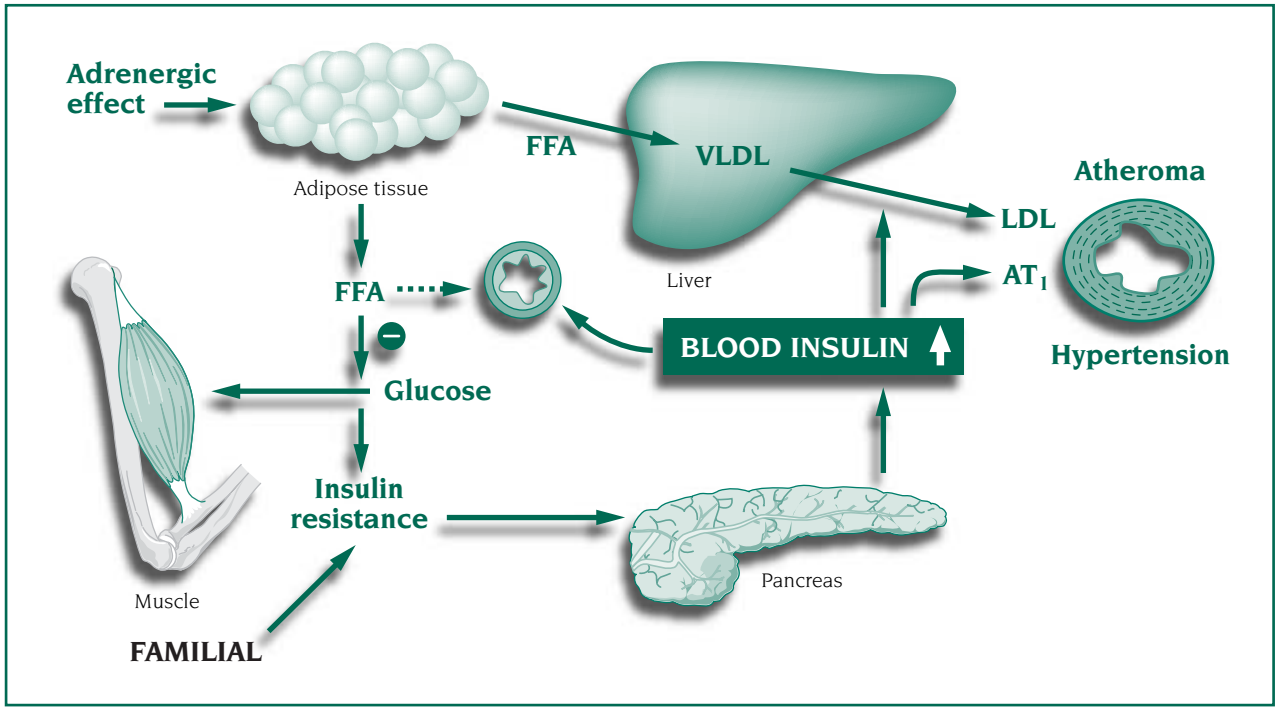


***Figure 2.*** *Mechanisms proposed to explain insulin resistance and its vascular complications. $AT_1$, angiotensin II receptor, subtype 1; FFA, free fatty acids; LDL, low-density lipoproteins; VLDL, very-low-density lipoproteins. Copyright © L.H. Opie, 1999.*

insulin resistance at the start.[11] Conversely, changing from a β-blocker to an angiotensin-converting enzyme (ACE) inhibitor may improve insulin resistance in a subset of hypertensives with marked insulin resistance.[12]

### Diabetic nephropathy

Diabetic nephropathy is the most common cause of hypertension in the less common type 1 insulin-deficient diabetic.[13] Yet it also contributes variably to the hypertension of type 2 diabetics.

## NONDRUG TREATMENT FOR ALL

### Lifestyle modification

A total revolution in the lifestyle of most obese type 2 diabetics is often required. The concept of insulin resistance has implications for the treatment of hypertension, because nonpharmacological treatment potentially improves insulin sensitivity.

• *Exercise.* Exercise training improves insulin sensitivity.[14] Muscular work enhances the transport of glucose into liver cells.[14] Exercise training is known to reduce BP in nondiabetics. Lack of exercise is now an established risk factor for coronary heart disease, which is known to be a serious complication of diabetes. Physical inactivity may be a risk factor for premature death in diabetics. Therefore, exercise (regular, aerobic) becomes doubly important. A simple recommendation would be running for 15 minutes or walking briskly for 30 minutes every day. In a multifactorial intervention trial, the aim was light-to-moderate exercise for at least 30 minutes, 3 to 5 times per week.[15]

• *Smoking.* Type 1 diabetic smokers have higher 24-hour BP values than nonsmokers, but data for type 2 diabetes are lacking. Both smoking and diabetes cause endothelial dysfunction, so that smoking should stop even in the absence of specific trial data.

• *Diet.* In diabetics, a diet high in complex carbohydrates, including fruit, vegetables, and fiber, helps to control blood sugar.[13]

• *Sodium restriction.* This step appears logical. There is increased sodium retention in diabetics. Elderly hypertensives, as a group, tend to retain sodium, even if they are not diabetic, so that sodium reduction may afford specific benefit in elderly diabetics (but this recommendation lacks supporting data).

• *Weight loss.* Important for nondiabetic hypertensives, weight loss is doubly important for diabetics, in whom it is part of diabetic control. Obesity and physical inactivity are

part of the picture of type 2 diabetes.[8] In diabetics, even modest weight reduction can improve blood pressure and control of blood sugar.[13] Overambitious aims on the part of the attending doctor may be counterproductive.

• *Multifactorial intervention.* Ideally, the above measures should be applied simultaneously and together with tight control of the diabetic status as monitored by fasting blood sugar or hemoglobin $A_{1c}$ status.[15]

## BLOOD PRESSURE LOWERING BY DRUGS

### Aims and means. Does it matter how the desired low level is reached?

The first aim must be to reduce the BP vigorously to a diastolic value of below 85 mm Hg, ideally to 82 mm Hg. This value comes from trial data,[1] and so can be regarded as reliable, but does not exclude the possibility that even lower BP levels might give greater benefit. Regarding systolic values, common sense and a variety of guidelines suggest that values of about 130 to 135 mm Hg are desirable, but, in the United Kingdom Prospective Diabetes Study (UKPDS), the attained systolic value was 144 mm Hg. To obtain such strict control would almost certainly require more than one agent in most diabetic hypertensives—up to three were used in UKPDS and more in the Hypertension Optimal Treatment (HOT) study.[2] But which is the best one to start with?

### Arguments for an ACE inhibitor as first choice

There are several good arguments for using ACE inhibitors first (together with lifestyle changes) in diabetic hypertensives, including: (i) the powerful preventive capacity of these agents in high-risk cardiovascular patients, including hypertensive diabetics, as shown in the still unpublished Heart Outcomes Prevention Evaluation (HOPE) study, in which the primary combined end point of cardiovascular death, myocardial infarction, and stroke was reduced by 25% in diabetic hypertensives; (ii) the extensive documentation of renoprotection by ACE inhibitors, in both diabetics with macroproteinuria and those with microalbuminuria, as well as in nondiabetic nephropathy; (iii) the better quality of life with ACE inhibitors than with other agents, including less erectile dysfunction (although not specifically reported in diabetics); and (iv) the possibility of protection from diabetic neuropathy or advancing retinopathy. Conversely, hypertensives treated without ACE inhibitors for an average of 9 years by "older" therapy, such as β-blockade, thiazide, or hydralazine, or combinations thereof, had a severalfold increase in the incidence of diabetes.[11]

For the above reasons, the present author argues that an ACE inhibitor should be the drug of first choice in diabetic hypertensives.
ACE inhibitors are among the first-line drugs for diabetic hypertensives recommended by the American National High Blood Pressure Education Program Working Group.[13] Even in the absence of overt hypertension (initial BP about 145-150/85-86 mm Hg), strict multifactorial intervention, including the use of ACE inhibitors in about 70% of the subjects, helps to prevent complications such as nephropathy, retinopathy, and autonomic neuropathy, as well as cardiovascular events, as shown by Parving's group.[15]

However, it must again be stated that to achieve the new low BP levels demanded by the international bodies and by trial data, combination therapy will often be required. There are powerful data favoring combination therapy. An ACE inhibitor should be an early (possibly the first) component of such combination therapy. In the view of the present author, the ideal combinations with an ACE inhibitor are low-dose diuretics and calcium channel blockers. Although these combinations have been used both in UKPDS[16] and in the HOT study,[2] yet formal proof of their efficacy compared with other combinations is awaited.

### β-Blockers: a surprise result

These agents are often regarded as less desirable in the treatment of diabetic hypertensives, because of the risks of increased glucose intolerance and increased hypoglycemia. However, in the very long-term UKPDS follow-up on type 2 diabetics, both captopril and atenolol achieved equally powerful antihypertensive effects and equal reduction in hard end points.[16] It needs to be recalled that β-blockers are powerful suppressors of the renin-angiotensin system, which would reduce the differences with ACE inhibitors. However: (i) there was decreased control of blood sugar in the atenolol groups, as shown by the need for grater doses of oral antidiabetic therapy; (ii) there were more dropouts in the atenolol groups ($P<0.0001$), with probably a greater incidence of impotence; and (iii) there was more weight gain in the atenolol groups.

The ACE inhibitor used in UKPDS was captopril, which is known to have a short duration of action with the risk of rebound activation of the renin-angiotensin system between doses, and without a good record in the management of nondiabetic

hypertension when given once or twice daily.[17] Therefore, the present author proposes that ACE inhibitors, preferably long-acting ones, should be agents of first choice in the therapy of hypertensive diabetics, even though this recommendation is only inferentially supported by the totality of data rather than by specific comparative trial data.

### Diuretics

In nondiabetic hypertensives, only low-dose, not high-dose, diuretics improve coronary heart disease and reduce total mortality.[6] In hypertensive whites treated with diuretics or diuretics and β-blockers, plasma glucose and insulin were higher after a glucose load,[18] particularly after the combination therapy. These findings may explain why treatment involving these drugs is associated with an increased incidence of diabetes mellitus.[11] Of note, however, is the fact that the diuretic doses used in those days were often high and very high, and these excessive doses were associated with increased mortality in an observational study. That low-dose diuretic treatment could be the basis of antihypertensive treatment in diabetics with systolic hypertension was shown in the Systolic Hypertension in the Elderly Program (SHEP) substudy, in which a low-dose diuretic was used as initial treatment, combined, if necessary, with atenolol or reserpine.[19]

### Calcium channel blockers

In mild hypertension in diabetics, an ACE inhibitor is preferred to a calcium blocker of the dihydropyridine (DHP) type.[20] In severe hypertension, it is often difficult to achieve adequate BP control without a calcium blocker. Combination therapy with at least two and often three or four drugs is usually needed. Two studies suggest that therapy starting with a DHP-type calcium blocker is highly effective in diabetic hypertensives.[2,21] Of note are the remarkable results of the SYSTolic hypertension in elderly in EURope trial (SYST-EUR) diabetic substudy, in which total mortality in the elderly with systolic hypertension was decreased by the agent nitrendipine.[3] A reservation is that this result reflects the adjusted relative risk of a rather small number of patients.

## DIABETIC NEPHROPATHY

### ACE inhibitor therapy in hypertensive type 1 diabetics with nephropathy

Hypertension usually reflects diabetic nephropathy, and "almost all patients with type 1 diabetes and overt nephropathy … are hypertensive."[22] Here, nephropathy is defined by the British Joint Committees as dipstick proteinuria or urine protein loss >200 mg per 24 hours.[22] BP increases as the urinary albumin loss increases. Are there specific advantages for ACE inhibition? Three persuasive studies show that ACE inhibition can fundamentally change the course of type 1 diabetic renal disease. There should be strict control of BP, to values of below 130/80 mm Hg, or even 125/75 mm Hg if there is proteinuria.[22] To achieve such low values, multiple drug therapy—which should include an ACE inhibitor titrated to maximal doses—will almost certainly be needed.

In type 2 diabetics, the Steno 2 trial has shown that BP reduction, usually by an ACE inhibitor, and as part of multifactorial intervention, can delay progression to nephropathy.[15] Also in type 2 diabetic hypertensives, the ACE inhibitor lisinopril was able to reduce albuminuria more than the equipotent and hypotensive dose of the β-blocker atenolol.[23]

### Renoprotective effect in the absence of hypertension

ACE inhibition specifically decreases the glomerular permeability to proteins by lessening the size of the selective pores. Here, the data of the recent EURODIAB Controlled trial of Lisinopril in Insulin-dependent Diabetes (EUCLID) study are of interest. Lisinopril was given over 24 months to type 1 diabetics with microalbuminuria, defined as a urinary albumin excretion of at least 20 μg/min (about 30 mg per day).[24] The final treatment difference, versus placebo, was 38.5 μg/min less protein loss in the lisinopril group. There was even a decrease in those with normal urine albumin values at the start.

## OTHER ASSOCIATED CONDITIONS THAT INFLUENCE THERAPY

### Ischemic heart disease

Diabetes predisposes to coronary heart disease, as does hypertension. Both cause coronary endothelial dysfunction. Hyperinsulinemia itself is an independent risk factor for ischemic heart disease. Even impaired fasting glucose, without overt diabetes, predisposes to recurrent ischemic events in survivors of myocardial infarction. If there is previous myocardial infarction, then β-blockers become the agents of choice in view of their proven effect in reduction in postinfarct mortality, also found in diabetics.[13]

### Isolated systolic hypertension with diabetes

Diuretics[19] and a DHP-type calcium blocker, nitrendipine,[3] have been

used with success in diabetics with isolated systolic hypertension (systolic BP >160 mm Hg, diastolic BP <90 mm Hg). These agents reduced stroke in their respective studies, but only the DHP-type calcium blocker was able to reduce overall mortality.[3] However, it must be emphasized that there has been no direct comparison between a diuretic and any calcium blocker in elderly diabetics with systolic hypertension, so that dogmatic recommendations cannot be made.

### Lipidemias: statins

Aggressive use of statins is now being advocated for diabetic hypercholesterolemia. This has relevance to hypertension from two points of view. First, hypercholesterolemia predisposes to endothelial dysfunction, which in turn may exaggerate or perpetuate hypertension. Second, hypertension predisposes to coronary heart disease. Postinfarct diabetic patients are more often hypertensive than nondiabetics, and the use of a statin such as pravastatin reduces cardiovascular events even if the initial cholesterol levels are only average.

### Congestive heart failure

The combination of ACE inhibitors, β-blockers, and diuretics will often be used, although this has not specifically been validated for diabetics.

### Impotence

ACE inhibitors are generally thought not to cause erectile problems, whereas β-blockers are often suspect. In nondiabetics, lisinopril (20 mg daily) and atenolol (100 mg daily) were compared in a crossover study, with the incidence of successful sexual intercourse as the end point. At first, both agents had inhibitory effects, but with prolonged therapy, near-normal function was restored in patients on lisinopril.[25] Thus, atenolol caused chronic and lisinopril only temporary sexual problems. These studies are relevant because of the known higher incidence of impotence in the diabetic population.[13]

## CONCLUSIONS

Diabetics have a number of important reasons for the increased incidence and seriousness of hypertension. Recent trials show that vigorous treatment of hypertension is able to reduce hard end points in type 2 diabetics. Treatment should be based on lifestyle modification, almost always supplemented by drugs. Each of the major categories of antihypertensives has been used in controlled trials as a first-line agent in diabetic hypertensives, with apparent success. Therefore, depending on the characteristics of the individual patient, therapy could be started with any of: (i) an ACE inhibitor; (ii) a cardioselective β-blocker; (iii) a low-dose diuretic; or (iv) a calcium channel blocker. Reasons are convincing for recommending ACE inhibitors as agents of first choice. However, in order to achieve the new low BP goals for diabetic hypertensives, which are low enough to reduce hard end points, combination therapy with two or three or even four drugs, of which one should be an ACE inhibitor, will often be required.

I wish to acknowledge those of my mentors who earlier carried out pioneering work in diabetes, including Sir Hans Krebs and Sir Ernst Chain.

A complete list of references (restricted by the Editors) is available from the author.

## REFERENCES

**1. UK Prospective Diabetes Study Group.**
*Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38.*
***BMJ.*** 1998;317:703-713.

**2. Hansson L, Zanchetti A, Carruthers SG, et al.**
*Effects 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.

**3. Tuomilehto J, Rastenyte D, Birkenhager WH, et al.**
*Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension.*
***N Engl J Med.*** 1999;340:677-684.

**4. Anonymous.**
*Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.*
***Diabetes Care.*** 1997;20:1183-1197.

**5. DECODE Study Group on behalf of the European Diabetes Epidemiology Study Group.**
*Will new diagnostic criteria for diabetes mellitus change phenotype of patients with diabetes? Reanalysis of European epidemiological data.*
***BMJ.*** 1998;317:371-375.

**6. Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure.**
*The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure.*
***Arch Intern Med.*** 1997;157:2413-2446.

**7. WHO-ISH Committee.**
*World Health Organization-International Society of Hypertension.Guidelines for the Management of Hypertension.*
***J Hypertens.*** 1999;17:151-183.

**8. Hypertension in Diabetes Study Group.**

*Hypertension in Diabetes Study (HDS): Prevalence of hypertension in newly presenting type 2 diabetic patients and the association with risk factors for cardiovascular and diabetic complications.*

***J Hypertens.*** 1993;11:309-317.

**9. Martin B, Warram J, Krolewski A, et al.**

*Role of glucose and insulin resistance in development of type 2 diabetes mellitus: results of a 25-year follow-up study.*

***Lancet.*** 1992;340:925-929.

**10. Egan BM, Hennes MM, Stepniakowski KT, et al.**

*Obesity hypertension is related more to insulin's fatty acid than glucose action.*

***Hypertension.*** 1996;27:723-728.

**11. Skarfors E, Lithell H, Selinus I, et al.**

*Do antihypertensive drugs precipitate diabetes in predisposed men?*

***BMJ.*** 1989;298:1147-1152.

**12. Berntorp K, Lindgarde F, Matiasson I.**

*Long-term effects on insulin sensitivity and sodium transport in glucose-intolerant hypertensive subjects when beta-blockade is replaced by captopril treatment.*

***J Hum Hypertens.*** 1992;6:291-198.

**13. National High Blood Pressure Education Program Working Group.**

*Report on Hypertension in Diabetes.*

***Hypertension.*** 1994;23:145-158.

**14. Perseghin G, Price TB, Petersen KF, et al.**

*Increased glucose transport-phosphorylation and muscle glycogen synthesis after exercise training in insulin-resistant subjects.*

***N Engl J Med.*** 1996;31:1357-1362.

**15. Gaede P, Vedel P, Parving HH, Pedersen O.**

*Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study.*

***Lancet.*** 1999;353:617-622.

**16. 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.

**17. Hansson L, Lindholm LH, Niskanen L, et al.**

*Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial.*

***Lancet.*** 1999;353:611-616.

**18. Swislocki ALM, Hoffman BB, Reaven GM.**

*Insulin resistance, glucose intolerance and hyperinsulinemia in patients with hypertension.*

***Am J Hypertens.*** 1989;2:419-423.

**19. Curb KD, Pressel SL, Cutler JA, et al.**

*Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension.*

***JAMA.*** 1996;276:1886-1892.

**20. Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RN.**

*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;338:645-652.

**21. Staessen JA, Fagard R, Thijs L, et al.**

*Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators.*

***Lancet.*** 1997;350:754-764.

**22. British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society endorsed by the British Diabetic Association.**

*Joint British recommendations on prevention of coronary heart disease in clinical practice.*

***Heart.*** 1998;80(suppl 2):S1-S29.

**23. Nielsen FS, Rossing P, Gall MA, Skott P, Smidt UM, Parving HH.**

*Impact of lisinopril and atenolol on kidney function in hypertensive NIDDM subjects with diabetic nephropathy.*

***Diabetes.*** 1994;43:1108-1113.

**24. EUCLID Study Group.**

*Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria.*

***Lancet.*** 1997;349:1787-1792.

**25. Fogari R, Zoppi A, Corradi L, et al.**

*Sexual function in hypertensive males treated with lisinopril or atenolol. A cross-over study.*

***Am J Hypertens.*** 1998;11:1244-1247.

# What is the most effective management of heart failure in diabetic patients?

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*Cardiovascular disease is by far the most important complication of diabetes. Strong evidence has accumulated to indicate that ischemic heart disease in diabetics, particularly in the post–myocardial infarction setting, is associated with an increased incidence of congestive heart failure (CHF), aggravating the outcome.*
*The prognosis of diabetics with CHF is poor and requires careful evaluation of patients to identify those liable to benefit most from early treatment. The pharmacological treatment of these patients does not fundamentally differ from that of the nondiabetic population (diuretics and angiotensin-converting enzyme [ACE] inhibitors), and should include optimal titration of treatment and use of maximum tolerated doses of ACE inhibitors and β-blockers. Results of ongoing trials will define whether angiotensin receptor blockers can further improve the long-term prognosis of this high-risk population.*

**Keywords:** heart failure; diabetes; ACE inhibitor; β-adrenergic blocker; angiotensin II receptor blocker

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The interest of researchers and cardiologists in congestive heart failure (CHF) has grown dramatically recently, due to several reasons. First, the increasing prevalence of this disease as a consequence of hypertension and chronic ischemic heart disease[1] has made CHF one of the most frequent causes of hospital admission, particularly in the elderly. Second, better understanding of the pathophysiological mechanisms responsible for its progression has made it possible to focus the diagnostic approach on diagnosing CHF at an asymptomatic or subclinical stage, where treatment is most effective. Finally, the development and availability of effective drugs has significantly improved prognosis and the cost-effectiveness of the therapeutic approach. This review summarizes the current evidence concerning the therapeutic approach to diabetic patients with CHF.

**SELECTED ABBREVIATIONS AND ACRONYMS**

| | |
|---|---|
| **AIRE** | Acute Infarction Ramipril Efficacy trial |
| **ARB** | angiotensin II receptor blocker |
| **ATLAS** | Assessment of Treatment with Lisinopril And Survival study |
| **CHARM** | Candesartan cilexetil in Heart failure Assessment of Reduction in Mortality and morbidity |
| **CONSENSUS** | COoperative North Scandinavian ENalapril SUrvival Study |
| **ELITE** | Evaluation of Losartan In The Elderly study |
| **GISSI-2** | Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico–2 |
| **MERIT-HF** | MEtoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure |
| **MOCHA** | Multicenter Oral Carvedilol Heart failure Assessment |
| **SAVE** | Survival And Ventricular Enlargement trial |
| **SOLVD** | Studies Of Left Ventricular Dysfunction |
| **TRACE** | TRAndolapril Cardiac Evaluation trial |
| **Val-HeFT** | Valsartan Heart Failure Trial |

## EVIDENCE OF INCREASED INCIDENCE OF CHF IN DIABETIC PATIENTS

From an epidemiological point of view, cardiovascular disease is by far the most important complication of diabetes; however, for years this fact has been surprisingly neglected. It is only recently that several large studies have provided in-depth information on the natural history of cardiovascular disease in diabetic patients.[2,3] Data from the Framingham study[2] have shown that diabetic subjects have a much higher risk of developing heart failure. Men aged 45 to 74 years had a twofold increase in risk and women a fivefold increase in risk, compared with their nondiabetic counterparts. These increases in risk persisted even when age, cholesterol, ischemic heart disease, blood pressure, and weight were taken into account. More recently, strong evidence has accumulated indicating that ischemic heart disease in diabetics, particularly after myocardial infarction (MI), is associated with an increased incidence of CHF. This has been documented even in the fibrinolytic era by data from the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico–2 (GISSI-2)[3] as well as other studies.

Two reasons may explain these observations: (i) the extent and severity of occlusive coronary artery disease, as indicated by more diffuse coronary atherosclerosis and a more frequent incidence of three-vessel disease; and (ii) the existence of a specific diabetic heart muscle disease, leading to systolic and diastolic dysfunction without evidence of coronary artery disease, which may be related to the duration of diabetes.[4] The underlying pathological abnormality appears to be collagen deposition within the heart muscle, which increases ventricular wall stiffness and is associated with diffuse microvascular changes including interstitial fibrosis, perivascular thickening and fibrosis, and microaneurysm formation.

## CHF AND MORTALITY IN DIABETIC PATIENTS

Analysis of crude mortality and morbidity rates in diabetic compared with nondiabetic patients with CHF indicates that diabetics have a worse outcome. Thus, a recent meta-analysis of major trials, including about 13 000 post-MI patients with symptomatic or asymptomatic left ventricular (LV) dysfunction from the Survival And Ventricular Enlargement trial (SAVE),[5] the Acute Infarction Ramipril Efficacy trial (AIRE),[6] the Trandolapril Cardiac Evaluation trial (TRACE),[7] and a subpopulation of the Studies Of Left Ventricular Dysfunction (SOLVD),[8] showed a mortality of 36.4% in diabetics and 24.7% in nondiabetics.[9] The relative role of concomitant risk factors in this setting remains undefined. Data from other recently completed trials in CHF confirm this trend despite differences in the overall underlying risk of death: in the Multicenter Oral Carvedilol Heart failure Assessment (MOCHA),[10] the mortality in patients not assigned to treatment with the study drug carvedilol was 30% in diabetic versus 9% in nondiabetic patients; in the MEtoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure (MERIT-HF),[11] the figures were 11.2% and 8.4%, respectively, and, in the Assessment of Treatment with Lisinopril And Survival (ATLAS) study,[12] these were 49% and 42%, respectively.

A recently published post-hoc analysis of TRACE has shown what the authors called an "accelerating" impact of diabetes on prognosis in post-MI patients with LV dysfunction, with the relative risk for mortality for diabetics increasing progressively over time.[13]

## EFFICACY OF PHARMACOLOGICAL TREATMENT

The therapeutic approach to CHF has progressively changed over the last decade. Although diuretics are still the mainstay of pharmacological treatment and digitalis continues to be recommended, particularly in the treatment of patients with atrial fibrillation, two classes of drugs have emerged as critical in the management of patients with heart failure: angiotensin-converting enzyme (ACE) inhibitors, which are now indicated in all classes of CHF patients, and β-blockers, whose efficacy in reducing morbidity and mortality has been documented in the latest trials. Angiotensin II receptor blockers are also currently under evaluation as an alternative or adjunct to ACE inhibitors to obtain a more effective blockade of the renin-angiotensin system. It is important to underline that all the available information relating to the use of these three classes of drugs in diabetic patients has been obtained by post-hoc subgroup analysis of trials on populations initially not selected for their diabetic status; furthermore, in all cases, diabetes was defined based on clinical history, without any distinction between type 1 diabetes and the more frequent type 2.[14]

### ACE inhibitors

The landmark studies in the evaluation of the efficacy of ACE inhibitors were performed in the eighties and early nineties,

when the COoperative North Scandinavian ENalapril SUrvival Study (CONSENSUS),[15] and the treatment[16] and prevention[17] arms of SOLVD were completed.
A subanalysis of SOLVD showed that ACE inhibitors were as effective in diabetics as in nondiabetics in reducing mortality and hospitalization rates.[8] More recently, the attention of researchers has shifted toward patients with overt CHF and/or with LV dysfunction resulting from acute MI. All the "long-term" studies enrolling patients with LV dysfunction some time after MI have shown a significant benefit of ACE inhibitor therapy, with a risk reduction in mortality of 19% to 27% over a 2.5- to 4-year period of follow-up. The aforementioned meta-analysis of the major trials in this setting indicated that the beneficial effect of ACE inhibitors documented in the overall population is also present when the analysis is limited to patients with a history of diabetes. More specifically, the absolute benefit per 1000 patients was 36 lives saved in the 10 501 nondiabetics and 48 in the 2282 diabetics.[9]

The issue of whether the efficacy of high- versus low-dose ACE inhibition would be different in patients with CHF and diabetes mellitus was addressed in a post-hoc analysis of ATLAS,[12] which compared the efficacy of high-dose (32.5-35 mg/day) versus low-dose (2.5-5 mg/day) lisinopril for a median duration of 46 months in 3164 patients, including 611 patients with diabetes mellitus, representing the largest cohort of patients with diabetes mellitus and CHF in a randomized, clinical trial to date. Patients with diabetes mellitus were defined as individuals receiving antihyperglycemic therapy at the time of randomization (20% of the total ATLAS study population). Patients with diabetes mellitus had a mean age of 65 years, and 78% were male. The etiology of CHF was ischemic (71%) or dilated cardiomyopathy (23%), or due to other causes (5%). The relative risk reduction in mortality of high versus low dose[5] was 14% in diabetic patients compared with 6% in nondiabetics. The tolerability of lisinopril at high doses was similar to that of low doses in patients with and without diabetes mellitus. These data, although not reaching the conventional level of statistical significance, suggest that the maximum tolerated dose of an ACE inhibitor is the most appropriate choice in diabetic patients with CHF.

## β-Blockers

For many years, β-blockers have been contraindicated in CHF patients, and even more so in diabetic patients, where the accentuation of altered lipid levels induced by these drugs and the fear of masking hypoglycemic episodes have been considered strong contraindications to their use, especially in patients treated with insulin. However, the pioneering work performed in the seventies and eighties, particularly by Scandinavian groups,[18] paved the way for their targeted use in patients with asymptomatic or overt CHF.
A retrospective analysis performed by Kjeskhus et al[19] showed that diabetic patients with CHF following MI benefited even more than those with preserved LV function. Recently, the investigators of the MOCHA trial[10] reported that carvedilol was associated with a dramatic decrease in mortality that was most evident in diabetic patients, with 6.1% mortality after a median of 6 months, compared with 30% mortality in the control group ($P<0.05$). Although the small sample size and the short follow-up of the study may have contributed by chance to this outstanding result, these data suggest that diabetic patients with CHF are among those who benefit most from treatment with β-blockers.
At variance with these data, in the recently published MERIT-HF trial, there was a nonsignificant trend toward a lower effect of the β-blocker metoprolol on mortality in diabetics compared with nondiabetics: indeed, in the former group, the confidence interval for the drug effect was over 1.

## Angiotensin II receptor blockers

Preliminary data obtained with irbesartan indicate that, unlike ACE inhibitors, angiotensin II receptor blockers (ARBs) may affect atrial natriuretic peptide levels and are able to significantly increase LV ejection fraction in diabetic patients with CHF,[20] which may have important pathophysiological implications. However, to date, there is a paucity of data on hard end points regarding the comparative effect of these agents in patients with diabetes: the only data presently available come from the Evaluation of Losartan In The Elderly–1(ELITE-1) study[21] in which the effects of losartan were compared with those of captopril in elderly patients with CHF. Although mortality was not the primary end point of the study, the data showed a statistically significant difference in mortality in favor of losartan in the overall population with a similar trend for diabetic patients (cardiovascular mortality: 4/87 [4.6%] in diabetics treated with losartan compared with 11/81 [13.6%] in those treated with captopril; relative risk 0.66; 95% confidence interval not available). The results of this trial prompted another study (ELITE-2), which was due to report at the end of 1999, designed to evaluate the

mortality advantage of losartan over captopril in elderly patients with CHF. The effect of ARBs in patients with CHF will be tested in two other trials, the Valsartan Heart Failure Trial [Val-HeFT][22] and the Candesartan cilexetil in Heart failure Assessment of Reduction in Mortality and morbidity [CHARM]), with a different study design from ELITE-2. Both trials will test the effect of ARBs versus placebo in symptomatic patients with CHF. These trials will determine whether ARBs plus ACE inhibitors are more efficacious than ACE inhibitors alone. CHARM will also evaluate the effects of candesartan in patients with preserved LV function and in those intolerant of ACE inhibitors.

## SO WHAT IS THE MOST EFFECTIVE MANAGEMENT OF HEART FAILURE IN DIABETIC PATIENTS?

Based on the data summarized in this review, the following main points relative to effective management of heart failure in diabetic patients may be highlighted:

• CHF is common in patients with diabetes.

• The prognosis of diabetic patients with CHF is poor and requires careful evaluation to identify those liable to benefit most from early treatment.

• The pharmacological treatment of diabetic patients with CHF does not fundamentally differ from that of the nondiabetic population, but requires optimization in order to ensure the most effective impact on prognosis.

• The approach of choice in diabetic patients with CHF includes the use of standard diuretics, angiotensin-converting enzyme (ACE) inhibitors, and digitalis, when required. Although specific trials testing the effects of diuretics in diabetic patients with CHF are not available, observations from clinical practice suggest that high-dose diuretics increase blood glucose levels in patients with type 2 diabetes. For this reason, careful titration of diuretic dosage is needed in these patients. Also necessary is the optimal titration of treatment and use of maximum tolerated doses of ACE inhibitors and β-blockers, particularly in diabetic patients with CHF.

• Results of ongoing trials will determine whether ARBs are able to further improve the long-term prognosis of this high-risk population.

• Finally, it is worth noting that statins in diabetic patients with CHF due to ischemic heart disease are not widely used. Here again, clinical trials do not provide specific information; however, common sense suggests that greater use of statins in this population of patients could further improve their prognosis.

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## REFERENCES

**1. The Task Force of the European Society of Cardiology.**
*Guidelines for the diagnosis of heart failure.*
***Eur Heart J.*** 1995;16:741-751.

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

**3. Zuanetti G, Latini R, Maggioni AP, Santoro L, Franzosi MG, GISSI-2 Investigators.**
*Influence of diabetes on mortality in acute myocardial infarction: data from the GISSI-2 study.*
***J Am Coll Cardiol.*** 1993;22:1788-1794.

**4. Jacoby RM, Nesto RW.**
*Acute myocardial infarction in the diabetic patient: pathophysiology, clinical course and prognosis.*
***J Am Coll Cardiol.*** 1992;20:736-744.

**5. Moyé LA, Pfeffer MA, Wun CC, et al, for the SAVE Investigators.**
*Uniformity of captopril benefit in the SAVE study: subgroup analysis.*
***Eur Heart J.*** 1994;15:2-8.

**6. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators.**
*Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure.*
***Lancet.*** 1993;342:821-828.

**7. Torp-Pedersen C, Kober L, Carlsen J, on behalf of the TRACE Study Group.**
*Angiotensin-converting enzyme inhibition after myocardial infarction: the Trandolapril Cardiac Evaluation Study.*
***Am Heart J.*** 1996;132:235-243.

**8. Shindler DM, Kostis JB, Yusuf S, et al, for the SOLVD Investigators.**
*Diabetes mellitus, a predictor of morbidity and mortality in the studies of left ventricular dysfunction (SOLVD) trials and registry.*
***Am J Cardiol.*** 1996;77:1017-1020.

**9. Flather MD, Kober L, Pfeffer MA, et al.**

*Meta-analysis of individual patient data from trials of long-term ACE-inhibitor treatment after acute myocardial infarction (SAVE, AIRE, and TRACE studies).*

***Circulation.*** 1997;96(suppl 8):I706.

**10. Bristow MR, Gilbert EM, Abraham WT, for the MOCHA Investigators.**

*Effect of carvedilol on left ventricular function and mortality in diabetic versus non-diabetic patients with ischaemic or non-ischaemic dilated cardiomyopathy.*

***Eur Heart J.*** 1996;17(suppl):78.

**11. MERIT-HF Study Group.**

*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.

**12. Rydén L, Armstrong P, Cleland JGF, et al, for the ATLAS Investigators.**

*High-dose ACE-inhibitor strategy is more effective than low-dose in diabetic patients with congestive heart failure.*

***J Am Coll Cardiol.*** 1999;33(suppl A):188. Abstract 825-3.

**13. Melchior T, Kober L, Madsen CR, et al.**

*Accelerating impact of diabetes mellitus on mortality in the years following an acute myocardial infarction.*

***Eur Heart J.*** 1999;20:973-978.

**14. American Diabetes Association.**

*Report of the expert committee on the diagnosis and classification of diabetes mellitus.*

***Diabetes Care.*** 1997;20:1183-1197.

**15. The CONSENSUS Trial Group.**

*Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS).*

***N Engl J Med.*** 1987;316:1429-1435.

**16. 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.

**17. The SOLVD Investigators.**

*Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fraction.*

***N Engl J Med.*** 1992;327:685-691.

**18. Waagstein F, Hjalmarson A, Varnauskas E, Wallentin J.**

*Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy.*

***Br Heart J.*** 1975;37:1022-1036.

**19. Kjeskhus J, Gilpin E, Cali G, Blackey AR, Henning H, Ross J Jr.**

*Diabetic patients and beta-blockers after acute myocardial infarction.*

***Eur Heart J.*** 1990;11:43-50.

**20. Tan LG, Chang DS, Lukman LF, et al.**

*Irbesartan decreases atrial natriuretic peptide levels and improves ejection fraction in diabetic patients with congestive heart failure.*

***Cardiovasc Drugs Ther.*** 1999;13:13.

**21. Pitt B, Segal R, Martinez FA, et al.**

*Randomized trial of losartan versus captopril in patients over 65 with heart failure.*

***Lancet.*** 1997;349:747-752.

**22. Cohn JN, Tognoni G, Glazer RD, Spormann D, Hester A.**

*Rationale and design of the Valsartan Heart Failure Trial: a large multinational trial to assess the effects of valsartan, an angiotensin-receptor blocker, on morbidity and mortality in chronic congestive heart failure.*

***J Card Failure.*** 1999;5:155-160.

# How can coronary artery disease and infarction be best managed in diabetics?

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*Coronary heart disease (CHD) remains the major factor for morbidity and mortality in diabetes. Management objectives—reduction in further events and complications—are identical to those in nondiabetics, as are the treatment strategies: antiplatelet agents, thrombolytics, cardioselective $\beta_1$-blockers, and angiotensin-converting enzyme inhibitors. Crucial diabetes-specific measures include optimization of glycemic control in both the long-term and acute myocardial infarction (using insulin-glucose infusion, with greatest benefit in patients not receiving insulin before infarction). Other strategies include aggressive lipid lowering and, on current evidence, coronary bypass rather than percutaneous revascularization. However, since even optimal management tends to be associated with poorer outcome than in nondiabetics, underutilization and inconsistent application of recommended therapies remain the key problems in current clinical practice.*

**Keywords:** coronary artery disease; myocardial infarction; type 2 diabetes; therapy; glycemic control

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Coronary heart disease (CHD) continues to be the major factor responsible for morbidity and mortality in patients with diabetes mellitus. The cumulative mortality due to coronary artery disease (CAD) in patients with type 1 diabetes mellitus by the age of 55 is 30% greater than in their nondiabetic counterparts. Sudden cardiac death occurs 50% more frequently in diabetic men and 300% more frequently in diabetic women. Early retrospective studies and recent prospective thrombolytic trials have consistently shown that diabetic patients experience greater mortality in the immediate peri–myocardial infarction (MI) period than nondiabetic patients. Multivessel CAD and a greater number of diseased vessels have been thought to be largely responsible for this difference in outcome. However, even when correcting for the extent of CAD, diabetics have more acute coronary events than nondiabetic individuals.

In addition to more extensive coronary atherosclerosis, other factors extrinsic to the atherosclerotic plaque itself conspire to increase the likelihood of plaque disruption with superimposed thrombosis in diabetics. In the presence of diabetes, there is increased platelet aggregation, impaired fibrinolysis, and enhanced coagulability, all of which may increase the chance of thrombosis in the setting of vascular injury. Also, the autonomic nervous system dysfunction present in a substantial number of type 2 diabetic individuals may contribute to plaque disruption and thrombosis. Cardiac parasympathetic fibers are affected before sympathetic fibers, leading initially to a relative increase in sympathetic tone that results in resting tachycardia and hypertension, thereby increasing myocardial oxygen demand.

It is not unexpected, therefore, that outcomes of diabetic patients differ considerably from those of nondiabetics. In this review, we will discuss treatment strategies shown to be effective in the secondary prevention of coronary events. We will also evaluate how treatment can reduce morbidity and mortality in the setting of acute MI.

## MEDICAL MANAGEMENT OF CORONARY ARTERY DISEASE IN DIABETICS

The standard of care for the treatment of CAD is guided by the results of multiple large clinical trials. Over the past 10 years, there has been a dramatic increase in survival rates for both diabetic and nondiabetic patients. The medical therapy of patients with CAD is multifactorial, comprising antithrombotic therapy (antiplatelet agents, anticoagulants, and thrombolytic agents), β-blockers, angiotensin-

converting enzyme inhibitors (ACEIs), and lipid-lowering drugs. Optimization of glycemic control at the time of MI is emerging as another potential important strategy to decrease morbidity and mortality in the diabetic population. Revascularization procedures, both percutaneous and surgical, also play a major therapeutic role in the management of these patients.

## Antiplatelet agents

Antiplatelet agents are the cornerstone of treatment for acute coronary syndromes. The three major classes of antiplatelet agents include cyclooxygenase inhibitors, adenosine disphosphate (ADP) receptor antagonists, and platelet glycoprotein IIb/IIIa receptor inhibitors.

### *Cyclooxygenase inhibitors*

Cyclooxygenase inhibitors are exemplified by aspirin, which blocks the formation of thromboxane $A_2$ in platelets by inhibition of cyclooxygenase. The overview by the Antiplatelet Trialists' Collaboration group found aspirin to be beneficial in the treatment of diabetic patients with cardiovascular disease or at a high risk for vascular disease. There was a reduction from 22.3% to 18.5% in the combined end point of vascular death, MI, or stroke in the aspirin group when compared with the control group. The benefit in the diabetic group was equivalent to that observed in the nondiabetic population.[1] Nevertheless, in the Second International Study of Infarct Survival (ISIS-2) trial, no additional reduction in mortality was shown in the diabetic group (160 mg of aspirin started at the time of diagnosis of MI),[2] though a relatively low dose of aspirin was used. In this study, the outcomes in diabetes relative to the different treatment came from a post-hoc analysis and could be subject to chance or error. Most investigators agree that aspirin should form part of the initial treatment of patients with acute coronary syndromes and is an effective secondary prevention therapy in patients with diabetes and CAD.

**SELECTED ABBREVIATIONS AND ACRONYMS**

| | |
|---|---|
| **ACEI** | angiotensin-converting enzyme inhibitor |
| **BARI** | Bypass Angioplasty Revascularization Investigation |
| **BIP** | Bezafibrate Infarction Prevention |
| **CABG** | coronary artery bypass graft |
| **CARE** | Cholesterol And Recurrent Events trial |
| **CATS** | Captopril And Thrombolysis Study |
| **DCCT** | Diabetes Control and Complications Trial |
| **DIGAMI** | Diabetic patients receiving Insulin-Glucose infusion during Acute Myocardial Infarction study |
| **FTT** | Fibrinolytic Therapy Trialists |
| **GISSI-2** | Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico–2 trial |
| **GLUT4** | insulin-sensitive muscle/adipose tissue glucose transporter |
| **GUSTO-1** | Global Utilization of Streptokinase and TPA for Occluded arteries–1 trial |
| **HMG-CoA** | 3-hydroxy-3-methylglutaryl coenzyme A |
| **ISIS-2** | Second International Study of Infarct Survival |
| **PCI** | percutaneous coronary intervention |
| **PTCA** | percutaneous transluminal coronary angioplasty |
| **SAVE** | Survival And Ventricular Enlargement trial |
| **TAMI** | Thrombolysis and Angioplasty in Myocardial Infarction trial |
| **UKPDS** | United Kingdom Prospective Diabetes Study |

### *ADP antagonists*

The thienopyridines ticlopidine and clopidogrel are both ADP antagonists, irreversibly inhibiting the ADP platelet receptor. Both ticlopidine and clopidogrel have been shown to be effective in the secondary prevention of acute coronary events in the general population, but no subgroup analysis in diabetics has been reported.[3]

### *Glycoprotein IIb/IIIa receptor inhibitors*

Glycoprotein IIb/IIIa receptor antagonists prevent the binding of fibrinogen to platelets, blocking platelet aggregation. Treatment with these drugs has resulted in lower rates of acute coronary events and fewer revascularization procedures in patients who present with unstable angina and non–Q-wave MI. Preliminary studies have suggested that treatment with heparin plus tirofiban, a specific inhibitor of the glycoprotein IIb/IIIa

receptor, in diabetic patients presenting with unstable angina or non–Q-wave MI, results in a significant and sustained reduction in major cardiac outcomes.[4]

## Thrombolytics

The benefit of thrombolytic therapy in patients with evolving Q-wave MI is well established. Diabetic patients appear to benefit from thrombolysis as much as nondiabetics.
ISIS-2 found that diabetic patients receiving streptokinase had a 31% improvement in survival compared with placebo; there was a 23% improvement in survival in the nondiabetic population.[2]
The Fibrinolytic Therapy Trialists' (FTT) Collaborative Group confirmed the benefit of thrombolysis in diabetic patients and demonstrated a 3.7% absolute reduction in mortality in diabetic patients compared with a 2.1% reduction in the control group.[5]
In these trials, thrombolytic therapy was not associated with hemorrhagic stroke compared with patients with no diabetes. It is important to note that, although diabetic patients respond to thrombolytic therapy relatively well, overall outcome is still worse. Subgroup analyses of the Global Utilization of Streptokinase and TPA for Occluded arteries (GUSTO-1), Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico–2 (GISSI-2), and Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trials have shown that short- and long-term mortality rates still remain 1.5 to 2 times higher in the diabetic population. The severity and extent of CAD, higher frequency of non–infarct zone ventricular dysfunction and congestive heart failure, and altered thrombotic-thrombolytic equilibrium may be factors responsible for the worse outcome in these patients.

## β-Blockers

β-Blockers provide important benefits for patients with acute and chronic coronary syndromes. Delivery of β-blockade in the setting of acute MI and in the postinfarction period reduces infarct size, infarct extension, recurrent ischemia, reinfarction, and sudden cardiac death. Several large trials have shown improved survival in patients receiving long-term administration of β-blockers after MI; the diabetic population even seems to benefit relatively more from β-blockade than nondiabetics. In the Bezafibrate Infarction Prevention (BIP) study, which involved more than 14 000 patients with chronic coronary artery disease, 19% had non–insulin-dependent diabetes. Total mortality at 3 years in diabetics receiving β-blockers was 7.8% compared with 14% in those who were not.[6] In the Miami trial, the reduction of mortality due to the early treatment of MI with metoprolol at 15 days was 4 times greater in diabetic patients compared with nondiabetics.[7] Despite their clear benefit, β-blockers are still underutilized, although the percentage of patients receiving this therapy has recently increased. Though impaired glucose tolerance and a blunted response to hypoglycemia can occur with β-blocker therapy, these events are rare when cardioselective agents ($\beta_1$-blockers) are used.

## Angiotensin-converting enzyme inhibitors

Several large randomized trials have shown that therapy with ACEIs in patients after an acute MI reduces infarct size, ventricular remodeling, sudden death, and mortality.
ACEIs have been shown to decrease mortality even more dramatically in diabetic individuals when compared with nondiabetics.[8] In the GISSI-3 trial, which included more than 2700 diabetic patients, early administration of the ACEI lisinopril significantly reduced both the 6-week and 6-month mortality in diabetics versus nondiabetics (6 weeks, 30% vs 5% reduction in mortality respectively; 6 months, 20% vs 0%, respectively). The GISSI-3 trial also suggested that diabetic patients derive more benefit than nondiabetics when treatment with an ACEI is begun within 24 hours of an acute MI.[9]

The benefits of ACEIs have been attributed to their effects on limiting ventricular remodeling, reducing infarct size, and promoting fibrinolysis. It has also been hypothesized that ACEIs may improve outcomes by decreasing further ischemic events. In the Survival And Ventricular Enlargement (SAVE) trial, there were 25% fewer MIs in those treated with ACEIs.[10] Similar findings were seen in the Captopril And Thrombolysis Study (CATS) where the use of ACEIs was associated with 37% fewer ischemic events.[11]

These beneficial effects of ACEIs in diabetic patients are probably multifactorial. ACEIs may facilitate ischemic preconditioning by potentiating bradykinin-dependent mechanisms. Bradykinin is a potent vasodilator and stimulates the release of several endothelium-derived vasodilators including nitric oxide and is an inhibitor of vascular smooth muscle cell proliferation. ACEIs may also decrease insulin resistance and improve glycemic control.

Taken together, these studies firmly establish the importance of the early administration of ACEIs as part of the regimen for the diabetic patient with an acute MI. ACEIs are also recommended in postinfarction patients with left ventricular dysfunction. In general, ACEIs are

underprescribed in these settings, particularly in the diabetic patient, due to fears about causing, or contributing to, hemodynamic instability, worsening azotemia, or hyperkalemia. However, ACEIs can be safely given to diabetic patients with similar clinical characteristics as in these trials.

## Lipid-lowering agents

There is strong evidence that a high plasma cholesterol level is a strong predictor of the risk of cardiovascular events in patients with diabetes. Therefore, aggressive lipid-lowering therapy would be expected to reduce this risk.[12]

The Cholesterol And Recurrent Events (CARE) subgroup analysis found that treatment with pravastatin reduced the risk of major coronary events in diabetic patients with preexisting coronary heart disease by 25%.[13] In a subgroup analysis of the Scandanavian Simvastatin Survival Study (4S), 202 diabetic patients with previous angina or MI were examined.[14] Simvastatin therapy was more relatively effective in decreasing coronary events in diabetic patients than in nondiabetics (55% vs 32%), although there was no difference in total mortality. In addition, there is recent evidence that the effect of statins in secondary prevention may extend beyond their cholesterol-lowering capabilities. These agents may also affect nonlipid mechanisms, such as modification of endothelial function, reducing vascular wall inflammatory responses, all of which may "stabilize" vulnerable plaques, decreasing thrombus formation. Statins are indicated for the treatment of patients with diabetes plus hypercholesterolemia and/or mild-to-moderate hypertriglyceridemia. Finally, the subset analysis of the Helsinki Heart Study compared the effects of gemfibrozil and placebo on coronary events in diabetic patients.[15] Diabetic patients receiving gemfibrozil had a lower coronary event rate than those receiving the placebo (3.4% vs 10.5%, respectively); the greatest benefit was found in those with baseline hypertriglyceridemia and low high-density lipoprotein (HDL) cholesterol.

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have emerged as the medication of choice for the treatment of hypercholesterolemia because they are well tolerated and efficacious. However, combination therapy with statins and fibrates may represent the optimal management when hypercholesterolemia is associated with hypertriglyceridemia and low HDL cholesterol in diabetic individuals with CAD.

## Importance of glycemic control

All of the above management issues are relevant for both diabetic and nondiabetic individuals. However, one additional factor that may be critical in defining outcome in diabetic patients is glycemic control. In general, poor glycemic control in type 2 diabetic patients may be associated with increased cardiac mortality and morbidity. Elevated glycosylated hemoglobin ($HbA_{1c}$) levels on admission to hospital are associated with a higher mortality rate after infarction. The Diabetes Control and Complications Trial (DCCT) examined the ability of intensive insulin treatment to reduce the risk and progression of end-organ complications in type 1 diabetes mellitus. Intensive glycemic control delayed the onset and slowed the progression of microvascular disease by 35% to 74%.[16] The United Kingdom Prospective Diabetes Study (UKPDS) investigated the impact of tight glycemic control on the incidence and severity of vascular complications in type 2 diabetic patients. Nearly 4000 newly diagnosed patients with type 2 diabetes were randomized either to conventional therapy or to intensive treatment—the latter employing sulfonylureas, metformin, and/or insulin with a target $HbA_{1c}$ less than 7.0%. Those in the intensive treatment arm had a 25% reduction ($P$=0.0099) in the risk of microvascular disease, as well as a 16% risk reduction ($P$=0.052) in MI and sudden death.[17] Since the UKPDS enrolled patients without clinical evidence of vascular disease, this degree of reduction in macrovascular events may not be experienced by diabetic patients with established CHD. It is also possible that type 2 diabetic patients with CHD might have derived more benefit from tight glycemic control; further clinical trials will be necessary to address this important issue.

Strict glycemic control during the acute phase of acute MI may protect the myocardium. The heart typically utilizes free fatty acids as its primary fuel for ATP generation. However, the ischemic myocardium utilizes glucose as its major source of ATP production. The most important glucose transporter in cardiac myocytes is GLUT4 (insulin-sensitive muscle/adipose tissue glucose transporter); insulin and other factors such as ischemia and acidosis stimulate the translocation of this transporter to the cell surface, thereby increasing glucose uptake by myocytes. In diabetic patients with ischemia, relative insulinopenia decreases translocation of GLUT4, resulting in decreased levels of intracellular glucose. Consequently, ATP production is depressed,

oxygen free radicals are generated, and myocardial oxygen consumption is increased. Myocardial contractile dysfunction ultimately occurs, with impaired performance of both infarcted and noninfarcted zones.[18]

The Diabetic patients receiving Insulin-Glucose infusion during Acute Myocardial Infarction (DIGAMI) study evaluated outcomes in 620 diabetic patients with an acute MI randomized to either intensive insulin therapy (insulin-glucose infusion for 24 hours followed by subcutaneous insulin therapy four times daily for >3 months) or standard treatment. Those receiving the intensive insulin regimen had a significant reduction in mortality at 1 year compared with those receiving conventional care (19% vs 26%). During the long-term follow-up, there was a relative mortality reduction of 28% when comparing control vs intensive groups. The greatest reduction in mortality was seen in patients who were not receiving insulin prior to the infarction.[19,20] If other studies support the findings of the DIGAMI trial, strict glycemic control may become standard therapy in diabetic patients with acute MI.

Sulfonylurea drugs are the most widely used agents to achieve glycemic control in patients with non–insulin-dependent diabetes. Possible cardiovascular adverse effects of some sulfonylureas have been discussed for three decades. However, this requires reconsideration in the light of recent large-scale prospective studies such as the Heart Outcomes Prevention Evaluation (HOPE) study[21] and the United Kingdom Prospective Diabetes Study (UKPDS).[22] In a recent retrospective data-based study, the use of sulfonylureas among patients undergoing coronary angioplasty for acute MI was associated with an increased risk of in-hospital mortality.[23] This is probably mediated through their inhibition of cardiac ATP-sensitive potassium ($K^+_{ATP}$) channels. The opening of $K^+_{ATP}$ channels is believed to facilitate ischemic preconditioning, a cardioprotective mechanism. The inhibition of this cardiac $K^+_{ATP}$ channel by some sulfonylureas may impair the myocardial preconditioning in the setting of ischemia, resulting in more extensive myocardial injury at the time of MI. Some sulfonylureas (glibenclamide and tolbutamide) have been shown in experimental studies to have a proarrhythmic and antiarrhythmic effect due to the role of the $K^+_{ATP}$ channel in regulating the duration of the cardiac action potential.[24]

## REVASCULARIZATION

In addition to the pharmacological therapies discussed above, coronary artery bypass surgery (CABG) and percutaneous coronary intervention (PCI) procedures have important roles in the management of patients with diabetes.
The indications for revascularization are similar in diabetic and nondiabetic patients. For either CABG or PCI, the presence of diabetes does not affect immediate procedural outcomes. However, higher rates of restenosis and early vein graft occlusion in diabetic patients increase the short- and long-term morbidity and mortality compared with nondiabetic patients. The restenosis rate is twice that found in nondiabetics for any percutaneous technique used. In a recent study, the 6-month angiographic restenosis rate after percutaneous transluminal coronary angioplasty (PTCA) was over 60% in diabetic patients with one fifth of the restenoses manifested as total occlusions that may result in a decline in left ventricular function. Total occlusion is a rare manifestation of restenosis in nondiabetic patients.

In the recently published Bypass Angioplasty Revascularization Investigation (BARI) study, patients with diabetes and multivessel CAD experienced a higher 5-year mortality when assigned to PTCA compared with CABG (34.5% vs 19.4%, $P$=0.0024). This suggests that for diabetic patients with similar characteristics to those randomized to BARI, CABG should be the initial therapeutic strategy.[25]

## CONCLUSIONS

The major objectives of the long-term management of diabetic patients with CAD are to reduce further events and complications. Antiplatelet agents, β-blockers, ACEIs, and lipid-lowering drugs represent the standard therapy for secondary prevention of CHD.
In addition, optimization of glycemic control at the time of MI should be considered another important strategy to decrease morbidity and mortality in the diabetic population. However, underutilization and inconsistent application of recommended therapies remain key problems in current clinical practice.

## REFERENCES

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

**2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group.**
*Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2.*
***Lancet.*** 1988;2:349-360.

**3. Balsano F, Rizzon P, Violi F, et al.**
*Anti-platelet treatment with ticlopidine in unstable angina, a controlled multicenter clinical trial.*
***Circulation.*** 1990;82:17-26.

**4. Theroux P, Ghannam A, Nasmith J, Barr E, Snapinn SM, Sax FL.**
*Improved cardiac outcomes in diabetic unstable angina/non–Q-wave myocardial infarction patients treated with tirofiban and heparin.*
***Circulation.*** 1998;98(suppl I):I359. Abstract 1889.

**5. Fibrinolytic Therapy Trialists' (FTT) Collaborative 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;11:162-165.

**6. 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. Bezafibrate Infarction Prevention (BIP) Study Group.*
***Am J Cardiol.*** 1996;77:1273-1277.

**7. Malmberg K, Herlitz J, Hjalmarson A, Rydén L.**
*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;10:423-428.

**8. Nesto RW, Zarich S.**
*Acute myocardial infarction in diabetes mellitus. Lessons learned from ACE inhibition.*
***Circulation.*** 1998;97:12-15.

**9. Zuanetti G, Latini R, Maggioni AP, Franzosi M, Santoro L, Tognoni G, on behalf of the GISSI-3 Investigators.**
*Effect of ACE inhibitor lisinopril on mortality in diabetic patients with acute myocardial infarction: data from the GISSI-3 study.*
***Circulation.*** 1997;96:4239-4245.

**10. Moye LA, Pfeffer MA, Wun CC, et al, for the SAVE Investigators.**
*Uniformity of captopril benefit in the SAVE study: subgroup analysis.*
***Eur Heart J.*** 1994;15:2-8.

**11. Van Den Heuvale AD, Van Gilst WH, Van Veldhuisen DJ, De Vries RJ, Dunselman PH, Kingma JH.**
*Long-term anti-ischemic effects of angiotensin-converting enzyme inhibition in patients after myocardial infarction.*
***J Am Coll Cardiol.*** 1997;30:400-405.

**12. Stamler J, Vaccaro O, Neaton JD, Wentworth D.**
*Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial.*
***Diabetes Care.*** 1993;16:434-444.

**13. Sacks FM, Pfeffer MA, Moye LA, et al.**
*The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol level.*
***N Engl J Med.*** 1996;335:1001-1009.

**14. Pyörälä K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Throrgeirsson G, for the Scandinavian Simvastatin Survival Study (4S) group.**
*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.

**15. Koskinen P, Manttari M, Manninen V, Huttunen JK, Hinonen OP, Frick MH.**
*Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study.*
***Diabetes Care.*** 1992;15:820-825.

**16. Diabetes Control and Complications Trial Research Group.**
*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.*** 1993,329:977-986.

**17. UK Prospective Diabetes Study Group.**
*Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33).*
***Lancet.*** 1998;352:837-853.

**18. Rodrigues B, Vam MC, McNeill JH.**
*Myocardial substrate metabolism: implications for diabetic cardiomyopathy.*
***J Mol Cell Cardiol.*** 1995;27:169-179.

**19. Malmberg K, Rydén L, Efendic S, et al.**
*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.

**20. Malmberg K, Norhammer 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.

**21. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators.**
*Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy.*
***Lancet.*** 2000;355:253-259.

**22. UK Prospective Diabetes Study (UKPDS) Group.**
*Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33).*
***Lancet.*** 1998;352:837-853.

---

**23. Garratt KN, Brady PA, Hassinger NL, Grill DE, Terzic A, Holmes DR.**
*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.

---

**24. Cole W, McPherson CD, Sontag D.**
*ATP-regulated $K^+$ channels protect the myocardium againt ischemia/reperfusion damage.*
***Circ Res.*** 1991;69:571-581.

---

**25. The 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;96:1761-1769.

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# Surfing the Heart

## *European Society of Cardiology – Medscape® Cardiology College and University Home Pages*

by Claudio Ceconi, MD

### College and University Home Pages

**http://www.mit.edu:8001/people/cdemello/geog.html**

Our first selection is a very simple, yet really useful site, which provides a periodically updated list linking to universities and colleges throughout the world. This is a unique resource constituting a powerful tool for searching the academic world on the web. The list is part of a personal home page (created by Miss Christina DeMello) hosted by the Massachusetts Institute of Technology server: the best example of what www can be!

### European Society of Cardiology

**http://www.escardio.org/**

**Escardio.org** is *the* home page of European cardiology. This site is strongly oriented toward popularizing the activities of European Society of Cardiology (ESC), but important scientific information is supplied as well. This site incorporates some of the most advanced web technology, and the result is very user-friendly. The left frame shows links to the eight major sections including the scientific and clinical information (guidelines, study groups, webcasts from the Annual Congress, etc), the journals of the ESC (full text), and information relevant to the different activities of the Society, including its Annual Congress. The top of the page features search tools and services (links, navigation tools, etc), including *Global Cardiology Network,* an advanced powerful search engine for sites of a series of member organizations (including the ESC, AHA, and ACC); and *ESC On-line Services,* a free web service allowing abstract submission and registration for ESC Congresses and meetings. With its advanced graphics, frequent updating, and services offered, **Escardio.org** is probably the most interesting and rich European site dedicated to cardiology.

### Medscape® Cardiology

**http://www.medscape.com/Home/Topics/cardiology/cardiology.html**

**Medscape.com** is not the site of a scientific society; nevertheless it probably offers the maximum that physicians can find on the web for free. The site is organized as a "web portal" linked to several different specialty sections, including cardiology. Medscape® Cardiology provides comprehensive and timely medical information, which includes journals *(American Heart Journal, Chest, Journal of Invasive Cardiology)* and features electronic pages, articles, press releases, and a remarkable coverage of major scientific congresses. Medscape® Cardiology also provides access to vast medical databases, including MEDLINE, searchable by a common engine, and extensive libraries of accredited programs of continuing medical education. An Editorial Board, which includes leading medical experts, is responsible for the contents of the site, and a process of peer-reviewing of articles is advertised. Registration is requested, and after logging on, the visitor is automatically linked to the area of interest. To date, **Medscape.com** has more than 1 200 000 registered members worldwide.

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**All sites accessed 15 February 2000**

# Trails of Discovery

## *Paradigms of discovery in diabetes mellitus*

**Arnold M. Katz, MD**

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Descriptions of diabetes mellitus are surprisingly ancient. The Ebers papyrus, dating from about 1500 BC, lists several means "to drive away the passing of too much urine." The term *diabetes*, which means "to pass through," as in a siphon, was coined in the 2nd century AD by Aretaeus the Cappadocian, who noted both "a melting down of the flesh and limbs into urine" and an unquenchable thirst "as if scorched by fire." Galen, a contemporary of Aretaeus, described diabetes as a disorder of the kidneys, which he called "hydrops of the chamber pot."

Knowledge of diabetes has evolved through several paradigms, which are shown in *Table I*. The **first paradigm,** of course, was recognition of the clinical syndrome. Polyuria, as noted above, was identified more than 3000 years ago. Its association with polydipsia was familiar to Roman physicians, as well as to Chinese and Japanese physicians of the 3rd century, who knew of the susceptibility of these patients to skin infections. Hindu physicians of the 5th and 6th centuries were also aware of this syndrome and noted that it occurred most often in obese individuals.

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Recognition of disordered carbohydrate metabolism, the **second paradigm** in this history, is often credited to Willis at Oxford *(Figure 1)*, who around 1680 found diabetic urine to be sweet. Willis is said to have left the urine of a diabetic on his windowsill, observed that flies were attracted to the dish, and tasted it to see what was so appealing to the insects. This allowed Willis to distinguish between diabetes *mellitus* (derived from the Greek word for honey) and diabetes *insipidus*, in which the urine has a bland (insipid) rather than a sweet taste. The sweetness of diabetic urine, however, had been known to Chinese and Japanese physicians of the 3rd century AD, Indian physicians of the 5th and 6th centuries AD, and the great Arab physicians of the 9th through 11th centuries. Proof that diabetes was a disorder of carbohydrate metabolism came in 1776, when Dobson isolated sugar crystals from evaporated diabetic urine.


***Figure 1.*** *Thomas Willis (1621-1675), English physician, a founder of the Royal Society (1662), was a pioneer in the study of the anatomy of the brain and diseases of the nervous system and muscle. He discovered the "circle of Willis" in the brain and wrote* Cerebri Anatomi *(1664). Said to have discovered that the urine of diabetics tasted sweet. Frontispice of* Opera Omnia, *Geneva, 1694.*

The **third paradigm** began with the discovery that the fundamental lesion lay in the pancreas. The exocrine role of this organ—to deliver digestive enzymes into the gut—was recognized in the 17th century when Wharton (1656) noted the histological similarity of the pancreas and salivary glands, and when Wirsung (1642), and later Santorini (1742), identified the duct that led from the pancreas into the lumen of the bowel. It was not until 1856, however, that Claude Bernard identified the role of pancreatic secretions in digestion when he observed that pancreatic juice emulsified oil and melted fat, and split these "fatty bodies" into fatty acids and glycerin.

A link between pancreatic dysfunction and diabetes mellitus was suggested by Cawley (1788), who described this clinical syndrome in

a patient with pancreatitis. Almost a century elapsed before this link could be confirmed experimentally because removal of the pancreas was difficult and few animals survived the procedure. Brunner, in 1863, noted polyuria and polydipsia in dogs after pancreatectomy, but missed the glycosuria. Proof of the causal link between loss of the pancreas and diabetes mellitus is credited to von Mering and Minkowski, who in 1889 repeated Brunner's experiment and found up to 5% sugar in the urine of pancreatectomized dogs.

The possibility that diabetes resulted from deficiency in the exocrine function of the pancreas was ruled out in 1893 by Hédon, who noted that a small amount of pancreatic tissue, even when not connected to the gut, prevented the appearance of diabetes. This led to the **fourth paradigm**, that the cause of diabetes was deficiency of the *internal* (endocrine) rather than the *external* (exocrine) secretion of the pancreas. The pancreatic islets *(Figure 2)* had been described in a doctoral thesis by Langerhans, who in 1869 discovered small clusters of translucent polygonal cells in the pancreas. Langerhans had no idea what these cells might be; others suggested they could be lymphatic follicles or embryonic rests. Languesse, on the basis of Hédon's observations, proposed in 1893 that a substance essential for carbohydrate metabolism was secreted directly into the blood by the islets of Langerhans, and, in 1901, Opie, at Johns Hopkins, described hyaline degeneration of the islets in a patient with diabetes mellitus. Additional descriptions of the link between pancreatic abnormalities and diabetes mellitus intensified the search for the substance that, when secreted into the bloodstream by the pancreas, regulated carbohydrate metabolism.

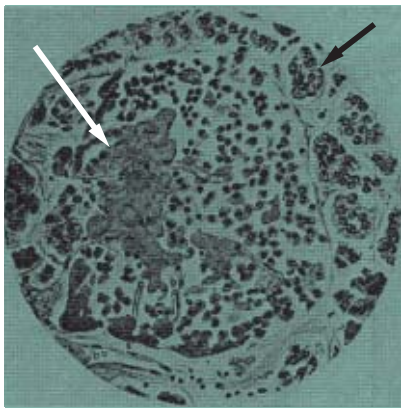

***Figure 2.*** *Sketch of histological slide of pancreas. Center, an islet of Langerhans; black arrow, acinar cells; white arrow, hyaline degeneration of an islet. Reproduced from: Opie EL. On the relation of the chronic interstitial pancreatitis to the islets of Langerhans and to diabetes mellitus.* J Exp Med. *1901;41.*

Between 1906 and 1921, at least six groups tried, but failed, to isolate the hormone produced by the islets of Langerhans (cited by Volk and Wellmann); I was told of two additional "almost" discoverers of insulin in 1953, when I was a medical student, and I am sure there are others. The active hormone, of course, was discovered in 1921 by Banting and Best, who recognized the likelihood that the active hormone was destroyed by digestive enzymes found in the acinar cells. Taking advantage of the fact that ligation of the pancreatic ducts destroyed the latter without affecting the islet cells, they were able to isolate this hormone from degenerated pancreas tissue 7 to 10 weeks after the duct was tied off. The term *insulin* had been proposed by de Mayer in 1909 and Sharpey-Shafer in 1916 for the then hypothetical carbohydrate-regulating hormone. Banting and Best initially preferred the term *isletin*, but the older term was chosen at the insistence of Macleod, who with Banting shared the 1923 Nobel Prize for discovering insulin.

Determination of the molecular structure of insulin, the **fifth paradigm**, took only a few decades. In 1953, Sanger described the amino acid sequence of insulin, for which he also received a Nobel Prize. This first description of the structure of a biological peptide helped lay the foundations of modern molecular biology.

The story told in this short article took a new and rather unexpected turn about a decade ago, when insulin was discovered to be a growth factor, which, when it binds to a tyrosine kinase receptor, stimulates the synthesis and translocation of a glucose transporter to the plasma membrane. This opened the **sixth paradigm** listed in *Table I*, which, because changes in proliferative signal transduction may explain the link between insulin deficiency and atherosclerosis, provides the basis for many discussions in this issue of *Dialogues in Cardiovascular Medicine.*

- A clinical syndrome: polyuria and polydipsia
- A disorder of carbohydrate metabolism: sweet urine
- A disorder of the pancreas: caused by pancreatitis
- An endocrine disorder: failure of the islets of Langerhans to secrete a substance into the bloodstream
- A molecular deficiency: lack of circulating insulin
- Impaired signal transduction: failure of a peptide-signaling pathway

***Table I.*** *Six paradigms of discovery involving diabetes mellitus.*

## FURTHER READING

Best CH. Epochs in the history of diabetes. In: Williams RH, ed. ***Diabetes.*** New York, NY: Harper and Row; 1960.

Major RH. ***Classic Descriptions of Disease.*** 3rd ed. Springfield, Ill: Charles C. Thomas; 1945.

Volk BW, Wellmann KF. Historical review. In: Volk BW, Arquilla ER, eds. ***The Diabetic Pancreas.*** 2nd ed. New York, NY: Plenum; 1985.

# Diabetes and the Heart

## *Summaries of Ten Seminal Papers*

1

Effects of an intravenous infusion of a potassium-glucose-insulin solution on the electrocardiographic signs of myocardial infarction

**D. Sodi-Pallares and others.** *Am J Cardiol.* 1962

2

Diabetes and cardiovascular disease. The Framingham study

**W.B. Kannel, D.L. McGee.** *JAMA.* 1979

3

Mortality from coronary heart disease and stroke in relation to degree of glycaemia: the Whitehall study

**J.H. Fuller and others.** *BMJ.* 1983

4

Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial

**J. Stamler and others.** *Diabetes Care.* 1993

5

NIDDM and its metabolic control predict coronary heart disease in elderly subjects

**J. Kuusisto and others.** *Diabetes.* 1994

6

Angiographic findings and outcome in diabetic patients treated with thrombolytic therapy for acute myocardial infarction: the GUSTO-I experience

**S.L. Woodfield and others.** *J Am Coll Cardiol.* 1996

7

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

**K. Pyörälä and others.** *Diabetes Care.* 1997

8

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

9

Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38)

**UK Prospective Diabetes Study Group.** *BMJ.* 1998

10

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 DIGAMI study

**K. Malmberg and others.** *Circulation.* 1999

Selection of seminal papers by
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Highlights of the years by **Dr P.B. Garlick**
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# Effects of an intravenous infusion of a potassium-glucose-insulin solution on the electrocardiographic signs of myocardial infarction

*D. Sodi-Pallares, M.R. Testelli, B.L. Fishleder, A. Bisteni, G.A. Medrano, C. Friedland, A. De Micheli*

***Am J Cardiol.*** 1962;9:166-181

This paper, which is a little more than a collection of case reports, was published in 1962 and its results were largely forgotten until the DIGAMI study (Diabetic patients receiving Insulin-Glucose infusion during Acute Myocardial Infarction) revealed strong evidence for the therapeutic effect of insulin and glucose during acute myocardial infarction.

The rationale of the study was as follows. After acute coronary artery occlusion, polarization of the myocardial fibers in the areas supplied by the occluded vessel is reduced. The degree of diastolic polarization varies in the different zones of the infarcted area and determines whether the zone is completely unexcitable (dead zone) or is activated with a delay (injury zone) or presents only alterations in its recovery or repolarization (ischemic zone). The concentration of potassium ions inside the fiber is about 30 times that outside the fiber. This ratio contributes to the resting polarization of the muscle fibers. There is considerable evidence to suggest that the polarization of the muscle fibers of the human heart is mainly due to the $K^+ / K_0^+$ ratio and to the permeability to $K^+$, which is sufficiently higher than the permeability to other ions to permit a transmembrane $K^+$ potential. Thus, any decrease in diastolic polarization must be followed by a decrease in the potassium ratio. Combined administration of potassium together with glucose and insulin was expected to increase resting polarization and affect potassium ratios within the myocardium. The protocol was to give 40 mmol of KCl and 20 units of soluble insulin together with 1000 mL of either 5% or 10% glucose. When less fluid was indicated, 500 mL of 10% glucose solution was used.

This study included a series of 7 case reports, in which all patients received this treatment and electrocardiograms were followed. The electrocardiogram was considered to be stabilized with this additional treatment. The authors were impressed by the absence or disappearance of arrhythmias together with an increased sense of well-being perceived by the patients. The authors concluded that the cardiac fiber membranes of infarcted zones still viable were actually helped towards restoring the normal permeability to potassium during the resting and recovery period following infarction.

This paper, largely forgotten for the past 30 years, has gained much more credence and respect following the DIGAMI study, which has shown a beneficial effect of glucose and insulin infusion in diabetic patients treated in the coronary care unit setting.

1962

44-year-old Nelson Mandela is jailed
for 5 years for activism;
Amnesty International is created;
and Jamaica gains independence
from Britain after 307 years

# Diabetes and cardiovascular disease. The Framingham study

*W.B. Kannel, D.L. McGee*

***JAMA.*** 1979;241:2035-2038

In this subset analysis from the father (or should I say mother) of all epidemiological studies—the Framingham study—diabetes was clearly defined as a major cardiovascular risk factor. This study reported on 20-year follow-up data from the Framingham epidemiological study, which had been in continuous operation since 1948. A cohort of 5209 men and women aged 30 to 62 years had been followed up biennially to determine in what way patients who go on to develop cardiovascular disease differ from those who remain free from the disease. Clinical cardiovascular end points were diagnosed from the biennial examinations as well as information from hospital admissions, medical examiners' reports, and other sources. Before diagnoses were made final they were submitted to a panel review of all the available information. The diagnosis of diabetes in the Framingham study was based on a history of treatment with oral hypoglycemic agents or insulin or the finding of elevated random blood sugar levels on two successive visits. People who exhibited these characteristics were then reviewed by the investigators and a final diagnosis of diabetes was made.

At the initial time of examination, 957 cases of cardiovascular disease were found among the 5209 patients of the study. In the course of the 20-year follow-up, the impact of diabetes on the major cardiovascular end points was determined by the sizes of the (age-adjusted) relative risks of disease for diabetics versus nondiabetics, and it was apparent that diabetes doubles the risk of total cardiovascular disease in men and almost triples it in women. The relative risk of cardiovascular death was also roughly doubled for men and more than tripled for women, even after age adjustment. The examination of the impact of diabetes on each of the major cardiovascular sequelae showed that its greatest effect in terms of relative risk was on intermittent claudication. Hypertension had the highest attributable risk for all of the cardiovascular events. Diabetes had the lowest attributable risk among males for all of the cardiovascular events except intermittent claudication. However, among females, the risk attributable to diabetes exceeded that of cigarette smoking. Thus, in summary, based on 20 years of surveillance of the Framingham cohort relating subsequent cardiovascular events to prior evidence of diabetes, a two- to threefold increased risk of clinical atherosclerotic disease was reported. The relative impact was substantially greater for women than for men.

This pivotal study was the first to really define and quantify diabetes as a major cardiovascular risk factor. Following this paper, numerous other prospective and mechanistic studies were launched to further examine the role of diabetes in the development of cardiovascular disease.

1979

Sony launches the first Personal Stereo in Japan; the success of Rubik's Cube makes its Hungarian inventor a multimillionnaire; and "The Deer Hunter" wins the Best Picture Oscar

# Mortality from coronary heart disease and stroke in relation to degree of glycaemia: the Whitehall study

*J.H. Fuller, M.J. Shipley, G. Rose, R.J. Jarrett, H. Keen*

***BMJ.*** 1983;287:867-870

For the first time in 1983, a study related risk of stroke in addition to coronary heart disease to the degree of glycemia. If the Framingham study was the father of all epidemiological studies, the Whitehall study was a close relation. In this prospective study, 18 403 male civil servants aged between 40 and 64 years were examined between 1967 and 1969. Their records were tagged at the central registry of the National Health Service and a virtually complete 10-year follow-up was available for comparison by the study group. At the initial screening examination, the following parameters were assessed: ECG, arterial blood pressure, body mass index, oral glucose tolerance test (OGTT, 50 g glucose, 2-hour blood glucose), and fasting lipid profile. For the purposes of the study 3 groups were defined: those who had diabetes (224 subjects); those with glucose intolerance (999 subjects with blood glucose concentrations at 2 hours ranging between 5.4 and 11.0 mmol/L); and a normoglycemic group (17 051 subjects whose blood glucose concentrations were below 5.4 mmol/L at 2 hours).

Mortality from stroke and coronary heart disease at 10 years showed a nonlinear relation to 2-hour blood glucose values with a significantly increased risk for glucose-intolerant subjects with concentrations between 5.4 and 11.0 mmol/L (and for diabetics [blood glucose greater than 11.1 mmol/L]). This study also confirmed the finding that systolic blood pressure was significantly related to the development of stroke as men in the highest systolic blood pressure quintile had 12 times, and treated hypertensive patients 25 times, the mortality from stroke compared with those in the lowest two quintiles. In addition, stroke mortality was increased by 2.5 times in those smoking 10 or more cigarettes a day compared with nonsmokers.

Multiple logistic analysis was performed with the variables significantly predictive of mortality from both stroke and coronary heart disease, ie, age, systolic blood pressure, treatment for blood pressure, and a blood glucose value of greater than 5.4 mmol/L. Within the glucose-intolerant and diabetic groups, the risk factors most strongly related to subsequent deaths from coronary heart disease were age and blood pressure, with less consistent relation to smoking, cholesterol concentrations, and obesity. Although several studies had reported, prior to this one, an increased prevalence of diabetes among cases of stroke, the definition of diabetes previously used was variable and the data patchy. Thus, this was the first large-scale study that showed increased death from stroke associated with elevated blood glucose values on the OGTT.

This very large epidemiological study was the first to show unequivocally that mortality rates from coronary heart disease had a nonlinear relation to 2-hour blood glucose values with a significantly increased risk in glucose-intolerant subjects and patients with diabetes. It also confirmed the important role of blood pressure, smoking, and cholesterol concentrations on cardiovascular disease in patients with diabetes. As a result of this study, clinical practice changed and people became much more aggressive in treating patients with glucose intolerance and, in particular, those with hypertension.

1983

Klaus Barbie is charged
with crimes against humanity;
"ET" encourages people to "phone home"
and wins four Oscars;
and Spanish artist Joan Miró dies, aged 90

# Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial

*J. Stamler, O. Vaccaro, J.D. Neaton, D. Wentworth*

***Diabetes Care.*** 1993;16:434-444

With its very large study population, the massive Multiple Risk Factor Intervention Trial (MRFIT) study had great advantages over others. Its disadvantage was the nonrandom way people were recruited. Participants in this cohort study were screened between 1973 and 1975 and followed up for an average of 12 years. The study cohort consisted of 361662 men aged between 35 and 57 who were seen at 20 centers throughout the USA. Participation in screening for this study was essentially on a voluntary basis. The most common recruitment procedure was from employment groups or communities. After exclusions for previous myocardial infarction and missing data, the final cohort was 347 978 men. Of these, 5163 had diabetes. Those with diabetes were on average 3 years older and had a slightly higher systolic blood pressure (+5.8 mm Hg). The percentage of the cohort reported as having diabetes increased progressively as age rose.

Over the 12-year follow-up, crude coronary heart disease and coronary vascular disease death rates were approximately 5 times higher in men with diabetes compared with men without diabetes. After adjustment for age, race, systolic blood pressure, serum cholesterol levels, and number of cigarettes per day, the relative risks were 3.2 for coronary heart disease and 3.0 for coronary vascular death. A significant independent association of diabetes with coronary vascular disease death was demonstrated. The effect of other risk factors was examined using univariate and multivariate analyses. Within each stratum homogeneous for cardiovascular risk, cardiovascular disease mortality was found to be considerably higher for patients with diabetes, including the stratum with optimal profile of the other risk factors (cigarette smoking, hypertension, and serum cholesterol).

Thus, the main findings of MRFIT confirmed that diabetes is a strong independent risk factor for cardiovascular disease mortality over and above the effect of serum cholesterol, blood pressure, and cigarette use. In addition, this large cohort study clearly showed that serum cholesterol, blood pressure, and cigarette smoking are significant strong, independent predictors of mortality in men with and without diabetes. The large cohort allowed this definitive study to answer the question as to the exact effect of diabetes on cardiovascular risk.

1993

Janet Reno becomes
the first female US Attorney General;
the Dallas Cowboys beat the Buffalo Bills 52-17
to win the Super Bowl;
and Italian car pioneer Ferrucio Lamborghini dies,
aged 76

# NIDDM and its metabolic control predict coronary heart disease in elderly subjects

*J. Kuusisto, L. Mykkanen, K. Pyörälä, M. Laakso*

***Diabetes.*** 1994;43:960-967

Scandinavia is an ideal environment in which to study epidemiological questions as by and large it can boast well-documented records and people there are relatively easy to contact and willing to take part in studies. Hence this study, which was set up to answer an important question, namely, whether non–insulin-dependent diabetes mellitus (NIDDM) and its metabolic control had an important influence on mortality and morbidity from ischemic heart disease in elderly subjects, is one of a whole series of important epidemiological studies that have originated from Scandinavia. This study was conducted in Kuopio in Eastern Finland, where 1910 subjects born between 1912 and 1921 were randomly selected from a population register that included all the inhabitants. A postal questionnaire was sent out and 83 subjects were excluded because they were too ill to participate. Eventually, 1299 of the eligible 1827 subjects participated with an overall participation rate of 71%. Subjects attended for a baseline examination between 1988 and 1989, and a follow-up study was then conducted between 1990 and 1991. Of the 1298 subjects participating in the baseline study, 1069 were nondiabetic and 229 had non–insulin-dependent diabetes mellitus (NIDDM). During the follow-up, 3.4% of the nondiabetics and 14.8% of the NIDDM subjects died of coronary heart disease (CHD) or had a nonfatal myocardial infarction. Surprisingly, the incidence of CHD or nonfatal myocardial infarction and all CHD events did not differ significantly between various glucose tolerance groups. Thus, men with abnormal glucose tolerance did not seem to have excess incidence of CHD events. In contrast, however, women with abnormal glucose tolerance had an excess incident rate of all CHD events. Odds ratios risk for CHD death, nonfatal myocardial infarction, and all CHD events, were 11.7, 4.7, and 5.4, respectively. In diabetic subjects, the risk factors were evaluated using univariate analysis. Glycosylated hemoglobin and duration of diabetes were the most significant baseline risk factors associated with both CHD and CHD events. Rates of both CHD death and all CHD in NIDDM subjects calculated by tertiles of glycosylated hemoglobin and duration of diabetes revealed striking results. There was a significant dose-response relationship between glycosylated hemoglobin as well as the duration of diabetes.

Thus, this study concluded that NIDDM in old age, particularly in women, was a strong risk factor for CHD mortality and morbidity. Furthermore, the study gave strong evidence for the importance of metabolic control in the risk of CHD events in elderly subjects with NIDDM. High glycosylated hemoglobin appears to predict CHD in elderly NIDDM subjects. The upshot was that based on the findings of this study, diabetologists adopted a more aggressive management of elderly patients in trying to achieve good metabolic control.

1994

Comet fragments crash into Jupiter
and produce giant fireballs;
US marines take control of Haiti
without firing a single shot;
and Rose Kennedy,
matriarch of the Kennedy clan,
dies, aged 104

# Angiographic findings and outcome in diabetic patients treated with thrombolytic therapy for acute myocardial infarction: the GUSTO-I experience

*S.L. Woodfield, C.F. Lundergan, J.S. Reiner, S.W. Greenhouse, M.A. Thompson, S.C. Rohrbeck, Y. Deychak, M.L. Simoons, R.M. Califf, E.J. Topol, A.M. Ross*

***J Am Coll Cardiol.*** 1996;28:1661-1669

GUSTO (Global Utilization of Streptokinase and TPA for Occluded arteries) was the first trial that sought to determine why patients with diabetes have approximately twice the mortality of nondiabetic patients in the setting of an acute myocardial infarction. The study was an invasive angiographic study and looked at patients receiving thrombolysis for acute myocardial infarction. Early infarct-related artery patency and reocclusion rates, together with global and regional ventricular function were measured. In addition, 30-day mortality rates were also recorded.

The GUSTO angiographic trial involved 2431 patients; of these, 12.8% (310) had diabetes and 2116 did not. However, the diabetic cohort had a significantly higher proportion of female and elderly patients, were more often hypertensive, came to hospital later, and had more congestive heart failure, together with a higher number of previous myocardial infarction and bypass surgery procedures. Surprisingly, 90-minute postthrombolysis patency flow grade rates in patients with and without diabetes were not significantly different. In addition, the reocclusion rates, although numerically different, did not reach statistical significance. Ejection fraction at 90 minutes after thrombolysis was similar, as was regional ventricular function. Diabetic patients had less compensatory hyperkinesia in the noninfarct zone compared with controls. Despite this, there was no significant difference in ventricular function at 5th- and 7th-day follow-up between the two groups. The striking finding, however, was that the 30-day mortality rate was 11.3% in diabetic patients versus 5.9% in nondiabetic patients.
This difference is similar to that reported in previous studies and was highly significant. These were the first data to demonstrate that diabetes is an independent determinant of early (30-day) mortality after myocardial infarction, even after adjustment for angiographic characterization. This study strongly supported numerous previous studies, which demonstrated increased mortality in patients with diabetes in the setting of acute myocardial infarction. Previously, the excess mortality had been attributed to larger infarct size, more frequent pump failure, as well as a greater number of comorbid conditions. This study using angiographic variables showed that the excess mortality noted in diabetic patients with acute myocardial infarction could not be explained by differences in early patency response to thrombolytic therapy, increased injury in response to ischemia and reperfusion, comorbid medical conditions, or the greater extent of coronary artery disease.

GUSTO showed that thrombolytic therapy was equally efficacious in restoring early infarct-related artery patency in patients with and without diabetes. There was no significant difference in the regional ventricular response to injury or reperfusion in diabetic patients compared with nondiabetic patients. However, there was a significantly blunted hyperkinetic response in the noninfarcted zone immediately after ischemic injury. This phenomenon may contribute to the increased prevalence of congestive heart failure seen in patients with diabetes and possibly to mortality. Thus, GUSTO clearly defined that thrombolysis in the early stages of acute myocardial infarction is as efficacious in diabetic as in nondiabetic patients, but that diabetes is nevertheless a powerful independent risk factor for early mortality. There is still a lot of work to be done in trying to find out why!

1996

Madeleine Albright becomes
the first female US Secretary of State;
hundreds of people are taken hostage
in the Japanese Embassy in Lima, Peru;
and a 6-year-old boy in the US
is punished for "sexual harassment,"
after kissing a schoolmate

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

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***Diabetes Care.*** 1997;20:614-620

Diabetic patients are subjected to an excessive coronary heart disease risk, which is thought to be in part explained by the adverse effects of diabetes on serum lipids and other general cardiovascular risk factors. Serum lipid abnormalities in type 2 diabetes are characterized by decreased high-density lipoprotein (HDL) cholesterol and elevated total and very-low-density lipoprotein (VLDL) triglyceride levels, whereas total cholesterol and low-density lipoprotein (LDL) cholesterol levels do not differ significantly from those of nondiabetic subjects. Serum total cholesterol has been shown to be a powerful predictor of coronary heart disease mortality and morbidity in both diabetic and nondiabetic patients. However, at every level of total cholesterol, diabetic patients have a 2 to 3 times higher coronary heart disease risk than nondiabetic subjects.

The Scandinavian Simvastatin Survival Study (4S) was designed to investigate the effect of cholesterol lowering with simvastatin on mortality and morbidity in patients with coronary heart disease. A total of 4444 patients with previous myocardial infarction or angina with serum cholesterol levels in the region of 5.5 to 8.0 mmol/L and serum triglycerides of less than 2.5 mmol/L were randomly allocated to receive simvastatin or placebo. This paper was a subgroup analysis of the data on diabetic patients included in the 4S study.

Recruitment and randomization of this study took place between 1988 and 1989. Patients were men and women aged between 35 and 70 years, with previous myocardial infarction or angina. Of the total of 4444 patients only 202 had diabetes. Of these, 97 were randomized to placebo and 105 to simvastatin. Over the 5.4-year median follow-up period, simvastatin treatment produced changes in the serum lipids in diabetic patients to a similar extent to those observed in nondiabetic patients. Over the whole course of the trial, simvastatin-treated nondiabetic patients had a reduction in total and LDL cholesterol of 24% and 34%, respectively, and this compared favorably with the diabetic patients in whom the reductions were 27% and 36%, respectively. HDL cholesterol and triglycerides altered by +8% and -9%, respectively, compared with +7% and -11% in the diabetic patients, respectively. Thus, simvastatin was effective in altering the lipid profile in a favorable way in diabetic and nondiabetic patients. Over the 5.4-year median follow-up period, the relative risk in simvastatin-treated diabetic patients from mortality was 0.5. The relative risk for a major coronary heart disease event was 0.45 and for any atherosclerotic event was 0.63. The corresponding relative risks in nondiabetic patients were similarly reduced, but if anything not quite as dramatically as those in diabetic patients. Allowing for the significantly reduced number of diabetic patients in the study, the findings are quite striking and show that the results of cholesterol lowering with simvastatin may indeed improve the prognosis of diabetic patients with coronary heart disease to a greater extent than nondiabetic subjects. Even though patients were excluded if they had elevated triglycerides, which is commonly found in diabetic patients, these results are highly meaningful and have altered clinical practice so that much more attention has been given toward the use of statins in diabetic patients. Similar results have been found from other large studies (such as the CARE trial published in *N Engl J Med* ).

1997

16-year-old Martina Hingis
becomes the youngest Wimbledon Champion
this century;
Paul McCartney receives a knighthood;
and fashion designer Gianni Versace
is shot dead in Miami

# 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;352:837-853

The UK Prospective Diabetes Study (UKPDS) was the largest and longest study in the history of diabetes. The study was conceived and designed in the 1970s and actually started in 1977, to finally report its major findings in 1998. When the UKPDS was designed, there was tremendous uncertainty about the appropriate metabolic goals for patients with type 2 diabetes. The aim was to find out whether an intensive policy of management with tighter blood glucose control had advantages over a less stringent strategy. The underlying hypothesis was that lowering the blood glucose to the normal range with any one of several medicines would reduce the likelihood of diabetes-related complications, specifically microvascular complications and the macrovascular events that are the major cause of mortality and morbidity in type 2 diabetes. The study design was complex; essentially, 3867 newly diagnosed type 2 diabetic patients from 23 participating centers were randomly allocated to an intensive treatment group, which could be with either a sulfonylurea, or insulin, or a less stringent policy starting with diet. Hard end points for both microvascular and macrovascular disease were used and all analyses were by intention to treat. Over the 10-year period of follow-up, glycosylated hemoglobin ($HbA_{1c}$) was 7.0% (6.2%-8.2%) in the intensively treated group, compared with 7.9% (6.9%-8.8%) in the conventionally treated group. In comparison with the conventionally treated group, the risk for any diabetes-related end point was 12% lower. Most of the risk reduction in any of the diabetes-related aggregate end points was due to a 25% risk reduction in microvascular end points. Most of this reduction was due to fewer patients requiring photocoagulation.

There were no obvious differences for any of the aggregate end points between the three therapies. Patients in the intensive group had more hypoglycemic episodes than those in the conventional group, and weight gain was significantly higher in the intensive group (mean 2.9 kg). Of these, patients assigned to insulin had a greater gain in weight (4 kg) than those assigned to chlorpropamide (2.6 kg) or glibenclamide (1.7 kg). Thus, the benefit of the intensive policy seems to be mainly due to improvements in microvascular outcomes with only borderline support for a decrease in macrovascular disease.

Thus, the main finding from this pivotal study is that intensive therapy of type 2 diabetes is beneficial, despite the associated weight gain (metformin is advantageous in not causing as much weight gain as insulin or sulfonylureas—but this was reported in a supplementary analysis (UKPDS 34). Despite the substantial reduction in the frequency of microvascular complications in the intensively treated group, there was no obvious benefit in terms of macrovascular disease. We can take heart, however, from the findings that insulin or insulin and sulfonylurea treatment did not have any detrimental effects on cardiovascular outcomes, reassuring those who questioned whether the intensive therapy methods of the Diabetes Control and Complications Trial (DCCT) could be directly translated to type 2 diabetes. Like all pivotal studies, as many questions were raised as were answered, and the study does not firmly establish the choice of any one therapy in the treatment of type 2 diabetes.

1998

British au pair Louise Woodward is convicted of manslaughter in Boston, USA; the Chicago Bulls win the NBA title with an 87-86 victory over Utah Jazz; and Nelson Mandela marries Grace Michel on his 80th birthday

# Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38)

*UK Prospective Diabetes Study Group*

***BMJ.*** 1998;317:703-713

Although only a subsidiary part of the main United Kingdom Prospective Diabetes Study (UKPDS), this study actually revealed the more dramatic results. Cardiologists have always been telling us diabetologists over many years that the circulation is more important than glucose homeostasis, and this study provides some grist to their mill! The subjects in this study included 1148 hypertensive patients with type 2 diabetes who were enrolled in the UKPDS. Patients were randomized to either tight blood pressure control (less than 150/85 mm Hg) with the use of an angiotensin-converting enzyme inhibitor or a β-blocker as main treatment, or to a less tight control group aiming at a blood pressure of less than 180/105 mm Hg. Patients were followed up for a median of 8.4 years and predefined clinical end points—fatal and nonfatal—related to diabetes and all-cause mortality were measured.

The results of this study show that the mean blood pressure during follow-up was significantly reduced in the group assigned to tight blood pressure control (144/82 mm Hg) compared with the group assigned to less tight control blood pressure (154/87 mm Hg). Reduction in risk in the group assigned to tight control compared with the less tight control group was 24% for diabetes-related end points and 32% for deaths related to diabetes. The reduction in stroke was 44% in the intensively treated group, and that in microvascular end points was 37%. The other major finding of this study was that after 9 years of follow-up, 30% of patients in the group assigned to tight control required three or more treatments to lower blood pressure to achieve the target. Thus, a policy of tight blood pressure control appears to reduce the risk of complications of diabetes to an even possibly greater extent than tight blood glucose control.

This paper has important implications for the treatment of diabetes and has led to all diabetologists being more aggressive in their blood pressure management. The other aspect of this study that has led to a wholesale change in clinical practice and perception of drug therapy is the fact that multiple combinations of different antihypertensive agents are often required for effective treatment of hypertension in patients with diabetes.

1998

Derek Bentley is cleared of murder
45 years after being hanged;
Britain celebrates 50 years of the NHS;
and Martin Luther King's killer,
James Earl Ray, dies in prison, aged 70

# 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 DIGAMI study

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

***Circulation.*** 1999;99:2626-2632

DIGAMI (Diabetic patients receiving Insulin-Glucose infusion during Acute Myocardial Infarction study) launched a thousand insulin prescriptions in every Coronary Care Unit across the world and made a large impact on the clinical care of diabetic patients undergoing myocardial infarction.

DIGAMI was a multicenter, randomized controlled study of the effect of intensive insulin treatment on mortality and morbidity in patients with diabetes presenting with acute myocardial infarction within the preceding 24 hours. Patients were stratified into four groups on the basis of risk classification and previous use of insulin. High-risk patients fulfilled more than two of the following criteria: age greater than 70 years, history of previous acute myocardial infarction, history of congestive heart failure, or ongoing treatment with digoxin. The predefined stratified groups were: (i) no insulin and low risk; (ii) no insulin and high risk; (iii) insulin and low risk; and (iv) insulin and high risk. Patients were randomized to intensive insulin treatment consisting of an insulin and glucose infusion, followed by multidose subcutaneous insulin for 3 months. Patients assigned to the control group received conventional treatment at the discretion of the physician in charge. Thrombolysis, β-blockade, and aspirin were initiated as soon as possible in the absence of any contraindications. The study population was followed for 1 year with outpatient visits scheduled at 3 and 12 months after randomization. In this paper, the long-term follow-up was described. The mean time of follow-up was 3.4 years (range 1.6-5.6 years) and did not differ between patients within the full strata. Of the 620 patients originally entered, 314 were allocated to the control and 306 to the intensive insulin treatment. The prevalence of previously undiagnosed diabetes in this group was 11% (66 out of the 620 patients). In total, 270 of the patients in the insulin group and 264 in the control group had definite acute myocardial infarction, with the number of possible acute myocardial infarctions being 9 and 23, respectively. At the time of hospital discharge, 80% of all patients were on aspirin, 70% were on β-blockers, and 31% received angiotensin-converting enzyme (ACE) inhibitors in addition to the antidiabetic treatment. During the long-term follow-up there were 240 deaths (39%); of these, 138 were in the control group (mortality 44%) and 102 were in the intensive group (mortality 33%). This difference was highly significant with a $P<0.011$. This corresponded to a relative mortality reduction of 28%. The most striking effect was observed in patients without prior insulin treatment and with a low predicted cardiovascular risk. Such subjects in the intensive group had a relative reduction of mortality of 51%. The association between long-term mortality and baseline glucometabolic state revealed striking associations. Among all patients, the most powerful predictors of an unfavorable outcome were a high blood glucose level at admission and onset of heart failure during the hospital phase.

The DIGAMI study and the papers that have resulted from it have brought cardiologists and diabetologists together with the single purpose of trying to improve blood glucose control in coronary care units (CCU). The workload of many diabetes specialist nurses has gone up considerably as a result of these observations, and in any hospital, the CCU is the site of many people being initiated onto insulin treatment. It is a salutary note that intensive insulin treatment achieves a reduction in mortality of diabetic patients with acute myocardial infarction almost equivalent to the use of thrombolysis. There is much theoretical evidence to support the intensification of blood glucose control in patients undergoing myocardial infarction, but it was not until the DIGAMI study addressed it with significant power that the true importance was formally demonstrated.

1999

Andre Agassi wins the French Open,
but not Wimbledon;
the 30th anniversary
of Apollo 11's moon landing is celebrated;
and Gwyneth Paltrow is in tears,
in a pink dress, at the Oscar ceremonies

# Diabetes and the Heart

## *Bibliography of One Hundred Key Papers*

**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.

---

**Andersson B, Waagstein F.**

*Spectrum and outcome of congestive heart failure in a hospitalized population.*
***Am Heart J.*** 1993;126:632-640.

---

**Aronson D, Bloomgarden Z, Rayfield EJ.**

*Potential mechanisms promoting restenosis.*
***J Am Coll Cardiol.*** 1996;27:528-535.

---

**Aronson D, Rayfield EJ, Cheseboro JH.**

*Mechanisms determining course and outcome of diabetic patients who have had acute myocardial infarction.*
***Ann Intern Med.*** 1997;126:296-306.

---

**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.

---

**Bjornholt JV, Erikssen G, Aaser E, et al.**

*Fasting blood glucose: an underestimated risk factor for cardiovascular death. Results from a 22-year follow-up of healthy nondiabetic men.*
***Diabetes Care.*** 1999;22:45-49.

---

**Calver A, Collier J, Vallance P.**

*Inhibition and stimulation of nitric oxide synthesis in the human forearm arterial bed of patients with insulin-dependent diabetes.*
***J Clin Invest.*** 1992;90:2548-2554.

---

**Caracciolo EA, Chaitman BR, Forman SA, et al, for the ACIP Investigators.**

*Diabetics with coronary artery disease have a prevalence of asymptomatic ischemia during exercise treadmill testing and ambulatory ischemia monitoring similar to that of nondiabetic patients.*
***Circulation.*** 1996;93:2097-2105.

---

**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 I):721.

---

**Chiariello M, Indolfi C, Cotecchia MR, Sifola C, Romano M, Condorelli M.**

*Asymptomatic transient ST changes during ambulatory ECG monitoring in diabetic patients.*
***Am Heart J.*** 1985;100:529-534.

---

**Chun BY, Dobson AJ, Heller RF.**

*The impact of diabetes on survival among patients with first myocardial infarction.*
***Diabetes Care.*** 1997;20:704-708.

---

**Clark CM Jr, Perry RC.**

*Type 2 diabetes and macrovascular disease: epidemiology and etiology.*
***Am Heart J.*** 1999;138:S330-S333.

**Colwell JA.**
*Aspirin therapy in diabetes.*
***Diabetes Care.*** 1997;20:1767-1771.

**Coutinho M, Gerstein HC, Wang Y, Yusuf S.**
*The relationship between glucose and incident cardiovascular events. A meta–regression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years.*
***Diabetes Care.*** 1999;22:233-240.

**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.

**Davi G, Catalano I, Averna M, et al.**
*Thromboxane biosynthesis and platelet function in type 2 diabetes mellitus.*
***N Engl J Med.*** 1990;322:1769-1774.

**Detre KM, Guo P, Holubkov R, et al.**
*Coronary revascularization in diabetic patients: a comparison of the randomized components of the Bypass Angioplasty Revascularization Investigation (BARI).*
***Circulation.*** 1999;99:633-640.

**Detry JM.**
*The pathophysiology of myocardial ischemia.*
***Eur Heart J.*** 1996;17(suppl G):48-52.

**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.

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

**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.

**Fava S, Azzorpadi J, Agius-Muscat H.**
*Outcome of unstable angina in patients with diabetes mellitus.*
***Diabet Med.*** 1997;14:209-213.

**Fein FS, Sonnenblick EH.**
*Diabetic cardiomyopathy.*
***Cardiovasc Drugs Ther.*** 1994;8:65-73.

**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 randomised trials of more than 1000 patients.*
***Lancet.*** 1994;343:311-322.

**Fisher BM, Frier BM.**
*Evidence for a specific heart disease of diabetes in humans.*
***Diabet Med.*** 1990;7:478-489.

**Garratt KN, Brady PA, Hassinger NL, Grill DE, Terzic A, Holmes DR Jr.**
*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.

**Gerich JE.**

*The genetic basis of type 2 diabetes mellitus: impaired insulin secretion versus impaired insulin sensitivity.*

***Endocr Rev.*** 1998;19:491-503.

---

**Gerstein HC.**

*Is glucose a continuous risk factor for cardiovascular mortality?*

***Diabetes Care.*** 1999;22:659-660.

---

**Gerstein HC, Pais P, Pogue J, Yusuf S.**

*Relationship of glucose and insulin levels to the risk of myocardial infarction: a case-control study.*

***J Am Coll Cardiol.*** 1999;33:612-619.

---

**Gerstein HC, Yusuf S.**

*Dysglycaemia and risk of cardiovascular disease.*

***Lancet.*** 1996;347:949-950.

---

**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;98:2513-2419.

---

**Granger C, Califf R, Young S, et al.**

*Outcome of patients with diabetes mellitus and acute mycardial infarction treated with thrombolytic agents.*

***J Am Coll Cardiol.*** 1993;21:920-925.

---

**Gray RP, Patterson DLH, Yudkin JS.**

*Plasminogen activator inhibitor activity in diabetic and nondiabetic survivors of myocardial infarction.*

***Arterioscler Thromb.*** 1993;13:415-420.

---

**Grines CL, Topol EJ, Califf RM, et al.**

*Prognostic implications and predictors of enhanced regional wall motion of the noninfarct zone after thrombolysis and angioplasty therapy of acute myocardial infarction. The TAMI study group.*

***Circulation.*** 1989;80:245-253.

---

**Gu K, Cowie CC, Harris MI.**

*Diabetes and decline in heart disease mortality in US adults.*

***JAMA.*** 1999;281:1291-1297.

---

**Gustavsson I, Torp-Pedersen C, Kober L, Gustavsson F, Hildebrandt P.**

*Effect of angiotensin-converting enzyme inhibitor trandolapril on mortality and morbidity in diabetic patients with left ventricular dysfunction after acute myocardial infarction.*

***J Am Coll Cardiol.*** 1999;34:83-89.

---

**Haffner SM.**

*Management of dyslipidemia in adults with diabetes.*

***Diabetes Care.*** 1998;2:160-178.

---

**Haffner SM.**

*The importance of hyperglycemia in the nonfasting state to the development of cardiovascular disease.*

***Endocr Rev.*** 1998;19:583-592.

---

**Haffner SM, Lehto S, Ronnemaa T, Pyörälä K, Laakso M.**

*Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction.*

***N Engl J Med.*** 1998;339:229-234.

---

**Hansson L, Lindholm LH, Niskanen L, 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) randomized trial.*

***Lancet.*** 1999;353:611-616.

---

**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.

---

**Hardin N.**

*The myocardial and vascular pathology of diabetic cardiomyopathy.*

***Cor Art Dis.*** 1996;7:99-108.

---

**Iwasaka T, Takahashi N, Nakamura S, et al.**

*Residual left ventricular pump function after acute myocardial infarction in NIDDM patients.*

***Diabetes Care.*** 1992;15:1522-1526.

---

**Jaarsma W, Visser CA, van Eenige MJ, et al.**

*Prognostic implications of regional hyperkinesia and remote asynergy of noninfarcted myocardium.*

***Am J Cardiol.*** 1986;58:394-398.

---

**Janand-Delenne B, Savin B, Habib G, Bory M, Vague P, Lassmann-Vague V.**

*Silent myocardial ischemia in patients with diabetes: who to screen.*

***Diabetes Care.*** 1999;22:1396-1400.

---

**Johnstone MT, Creager SJ, Scales KM, Cusco JA, Lee BK, Creager MA.**

*Impaired endothelium-dependent vasodilation in patients with insulin-dependent diabetes mellitus.*

***Circulation.*** 1993;88:2510-2516.

---

**Kannel WB, McGee DL.**

*Diabetes and cardiovascular disease. The Framingham study.*

***JAMA.*** 1979;214:2035-2038.

---

**Kendall MJ, Lynch KP, Hjalmarson A, Kjekshus J.**

*Beta-blockers and sudden cardiac death.*

***Ann Intern Med.*** 1995;123:358-367.

---

**King H, Aubert RE, Herman WH.**

*Global burden of diabetes 1995-2025. Prevalence, numerical estimates and projections.*

***Diabetes Care.*** 1998;21:1414-1431.

---

**Klieger R, Miller J, Bigger J, Moss A.**

*Decreased heart rate variability and its association with increased mortality after acute myocardial infarction.*

***Am J Cardiol.*** 1987;59:256-262.

---

**Kwaan H.**

*Changes in blood coagulation, platelet function and the plasminogen-plasmin system in diabetes.*

***Diabetes.*** 1992;41:32-35.

---

**Lundbäck K.**

*Diabetic angiopathy: a specific vascular disease.*

***Lancet.*** 1954;2:377-379.

---

**Malmberg K.**

*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.

**Malmberg K, Herlitz J, Hjalmarsson A, Rydén L.**

*Effects on 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.

---

**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.

---

**Malmberg K, Rydén L, Efendic S, Herlitz J, Nicol P, Waldenstrom A, Wedel H, Welin L.**

*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.

---

**Malmberg K, Rydén L, Wedel H.**

*Calcium antagonists, appropriate therapy for diabetic patients with hypertension?*

***Eur Heart J.*** 1998;19:1269-1272.

---

**Margolis J, Kannel W, Feinlieb M, Dawber T, McNamara P.**

*Clinical features of unrecognized myocardial infarctions—silent and symptomatic.*

***Am J Cardiol.*** 1973;32:1-7.

---

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

*Factors responsible for impaired fibrinolysis in obese subjects and NIDDM patients.*

***Diabetes.*** 1994;43:104-109.

---

**Miettinen H, Lehto S, Salomaa V, et al.**

*Impact of diabetes on mortality after the first myocardial infarction. The FINMONICA Myocardial Infarction Register Study Group.*

***Diabetes Care.*** 1998;21:69-75.

---

**Moye L, Pfeffer M, Wun C, et al.**

*Uniformity of captopril benefit in the SAVE study: subgroup analysis.*

***Eur Heart J.*** 1994;15(suppl B):2-8.

---

**Nathan DM.**

*Long-term complications and diabetes mellitus.*

***N Engl J Med.*** 1993;328:1676-1685.

---

**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 Intern Med.*** 1988;108:170-175.

---

**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.

---

**Niskanen L, Turpeinen A, Penttila I, Uusitupa MI.**

*Hyperglycemia and compositional lipoprotein abnormalities as predictors of cardiovascular mortality in type 2 diabetes: a 15-year follow-up from the time of diagnosis.*

***Diabetes Care.*** 1998;21:1861-1869.

---

**No authors listed.**

*Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.*

***Diabetes Care.*** 1997;20:1183-1197.

**O'Connor CM, Hathaway WR, Bates ER, et al.**

*Clinical characteristics and long-term outcome of patients in whom congestive heart failure develops after thrombolytic therapy for acute myocardial infarction: development of a predictive model.*

***Am Heart J.*** 1997;133:663-673.

---

**O'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.

---

**Opie LH.**

*Proof that glucose-insulin-potassium provides metabolic protection of ischaemic myocardium.*

***Lancet.*** 1999;353:768-769.

---

**Pais P, Pogue J, Gerstein H, et al.**

*Risk factors for acute myocardial infarction in Indians: a case-control study.*

***Lancet.*** 1996;348:358-363.

---

**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.

---

**Ranjadayalan K, Umachandran V, Ambepityia G, Kopelman PG, Mills PG, Timmis AD.**

*Prolonged anginal perceptual threshold in diabetes: effects on exercise capacity and myocardial ischemia.*

***J Am Coll Cardiol.*** 1990;16:1120-1124.

---

**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.

---

**Rodrigues B, Cam MC, McNeill JH.**

*Metabolic disturbances in diabetic cardiomyopathy.*

***J Mol Cell Biol Biochem.*** 1998;180:53-57.

---

**Rodrigues B, McNeill JH.**

*The diabetic heart: metabolic causes for the development of a cardiomyopathy.*

***Cardiovasc Res.*** 1992;26:913-922.

---

**Soläng L, Malmberg K, Rydén L.**

*Diabetes mellitus and congestive heart failure. Future knowledge needed.*

***Eur Heart J.*** 1999;20:789-795.

---

**Stamler J, Vaccaro O, Neaton JD, Wentworth D.**

*Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial.*

***Diabetes Care.*** 1993;16:434-444.

---

**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.

---

**Suskin N, McKelvie RS, Roteaus J, Sigouin C, Wiece KE, Yususf S.**

*Increased insulin and glucose levels in heart failure.*

***J Am Coll Cardiol.*** 1998;3(suppl):249A.

**Takahashi N, Iwasaka T.**

*Left ventricular regional function after acute anterior myocardial infarction in diabetic patients.*

***Diabetes Care.*** 1989;12:630-635.

---

**The CONSENSUS Trial Study Group.**

*Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS).*

***N Engl J Med.*** 1987;316:1429-1435.

---

**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.

---

**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.

---

**Ting HH, Timimi FK, Boles KS, Creager SJ, Ganz P, Creager MA.**

*Vitamin C improves endothelium-dependent vasodilation in patients with non–insulin-dependent diabetes mellitus.*

***J Clin Invest.*** 1996;97:22-28.

---

**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.

---

**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.

---

**UK Prospective Diabetes Study Group. U.K.**

*Prospective Diabetes Study 27. Plasma lipids and lipoproteins at diagnosis of NIDDM by age and sex.*

***Diabetes Care.*** 1997;20:1683-1687.

---

**UK Prospective Diabetes Study Group.**

*Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38.*

***BMJ.*** 1998;317:703-713.

---

**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.

---

**Wikström G, Malmberg K, Rydén L.**

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

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

---

**Willerson JT.**

*Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease.*

***Circulation.*** 1996;94:1194.

---

**Williams SB, Cusco JA, Roddy MA, Johnstone MT, Creager MA.**

*Impaired nitric oxide–mediated vasodilation in patients with non–insulin-dependent diabetes mellitus.*

***J Am Coll Cardiol.*** 1996;27:567-574.

---

**Williams SB, Goldfine AB, Timimi FK, Ting HH, Roddy MA, Creafer MA.**

*Acute hyperglycemia attenuates endothelium-dependent vasodilation in humans in vivo.*

***Circulation.*** 1998;97:1695-1701.

---

**Wingard DL, Barett-Connor E.**

*Heart disease in diabetes.*

In: Harris MI, Cowie CC, Stern M, Boyko E, Reiber G, Bennet PH, eds. ***Diabetes in America.*** 2nd ed. Washington, DC: US Government Printing Office; 1995:429-448.

---

**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.

---

**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.

---

**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.

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**2.** Darling RC, Brewster DC, Ottinger LW. Autopsy study of unoperated abdominal aortic aneurysms: the case for early resection. *Circulation.* 1977;56(suppl II):II161-II164.

**3.** Schulman JL. Immunology of influenza. In: Kilbourne ED, Alfade RT, eds. *The Influenza Viruses and Influenza.* Orlando, Fla: Academic Press Inc; 1975:373-393.

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