Treating the diabetic patient with coronary disease

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Diabetes is an independent risk factor for the development of coronary heart disease among men and women. The overall mortality risk is increased two- to three-fold in men and three- to five-fold in women[1,2].

Several risk factors contribute to the poorer outlook for diabetics. Diabetic patients are more prone to develop myocardial heart failure, and the existence of a specific diabetic heart disease, as a separate nosological entity, rather than diffuse ischaemic scarring, has been suggested[3].

The degree of coronary vascular involvement is more extensive in diabetics than non-diabetics with more widespread and peripheral location, which is reflected in the frequent occurrence of small and silent infarcts[4]. The Framingham study observed 39% silent infarcts among diabetics compared to 22% among non-diabetics[5]. Silent ischaemia during exercise testing is also more frequent among diabetics and may therefore involve loss of sensor function[6]. Diabetic patients with coronary heart disease demonstrate marked dysfunction of the autonomic system with myocardial sympathetic dysregulation in addition to loss of vagal reflexes[7]. As a result, resting heart rate is increased with loss of diurnal variation in heart rate. Elevation of heart rate increases myocardial oxygen demand and reduces myocardial perfusion time due to shortened diastole which may amplify any ischaemic event. This condition is closely associated with silent ischaemia, increased risk of myocardial infarction and cardiovascular death, especially sudden death[7].

Hyperglycaemia may increase the risk of coronary heart disease as a result of dyslipoproteinemia, increased oxidative stress, non-enzymatic glycosylation and endothelial dysfunction, and by causing a prothrombotic state. In addition microvascular complications develop in many patients with insulin-dependent diabetes (IDDM) which is independent of the occurrence of coronary heart disease. Patients with insulin-resistant non-insulin dependent diabetes mellitus (NIDDM) have a strong propensity for atherosclerotic disease.

Long-term treatment

Beta-blocker treatment can be used to reduce the resting heart rate in diabetic patients with autonomic dysfunction, and several clinical trials have demonstrated their marked effect on the risk of cardiovascular death after myocardial infarction. In long-term studies, mortality is reduced by 33% in non-diabetic patients treated with beta-blockers compared to 48% in similarly treated patients with diabetes[4]. Risk reduction appears proportional to heart rate reduction[8]. However, the risk of prolonged hypoglycaemia and masking of symptoms in diabetic patients treated with beta-blockers is real, but its occurrence is rare and beta-blocker treatment should not be withheld because of the possibility of hypoglycaemia.
In a previous post-myocardial infarction study, in diabetic patients randomized to intensified health education, improved metabolic control and coronary risk factor intervention with and without clofibrate acid the effect on the incidence of recurrent myocardial infarction or myocardial ischaemia was no different from a control group receiving standardized care at a diabetic outpatient clinic. Unfortunately, however, the improved control of carbohydrate metabolism resulted in a slight increase in lipids. Clofibrate acid reduced triglycerides but not the incidence of ischaemic heart disease. Diabetics in general have high triglycerides, very low density lipoproteins (VLDL) and low high-density lipoprotein (HDL) cholesterol levels, while total and low density lipoprotein (LDL) cholesterol is the same as for non-diabetics. However, LDL appears to be more atherogenic than triglycerides among diabetics. Hyperglycaemia alters LDL particles by glycating them, making them more likely to oxidize. With the introduction of HMG CoA reductase inhibitors, physicians were able to obtain a large reduction in plasma LDL with very few adverse effects.

The Scandinavian Simvastatin Survival Study included 202 diabetic patients with coronary disease. Simvastatin reduced LDL cholesterol by 36% and the risk of major coronary heart disease event by 55%, which compares to 35% and 32%, respectively, in non-diabetic patients. Both relative and absolute risk reduction was larger than that obtained for non-diabetics, although these differences did not reach statistical significance. While intensified insulin treatment has been shown to reduce development of microvascular complications in patients with IDDM, its effects on the development of atherosclerosis has not been established.

Optimization of glucose metabolism by insulin treatment may reduce platelet reactivity and improve fibrinolytic activity; however, as yet it is not known if this translates into reduced numbers of thrombotic events. In the recent BARI trial, it became evident that death rate among diabetics was much higher among patients treated with PTCA (35%) compared to those treated with CABG (19%). This may suggest that thrombotic or thrombolytic mechanisms are more important among diabetics than non-diabetics, but it remains to be demonstrated how optimal glucose control will affect these events. Animal experiments suggest that ischaemic myocardial damage is reduced by glucose-insulin-potassium treatment during coronary revascularization. Antiplatelet treatment with aspirin does not seem to be particularly efficient in diabetics. As of today, there is solid evidence that adjustment of lipid disorders and of autonomic dysfunction, by lipid-lowering interven-

tion and by beta receptor blockade has markedly improved the long-term prognosis in diabetics with stable ischaemic heart disease, while the effect of glycaemic control on atherosclerotic events is still controversial.

**Treatment of acute myocardial infarction**

Following the introduction of thrombolytic therapy, mortality has reduced in both non-diabetics and diabetic patients. However, mortality still remains higher among non-diabetics.

In acute myocardial infarction, early mortality and reinfarction are almost twice as high in diabetics than non-diabetics. Marked sympathetic stimulation takes place at the onset of the myocardial infarction, resulting in increased heart rate, lipolysis and elevation of free fatty acids.

Increased heart rate during evolving myocardial infarcts carries an independent risk which is amenable to beta-receptor blockade. The pooled results from trials with beta-blocker treatment of acute myocardial infarction demonstrate a 13% reduction of mortality in non-diabetic patients compared to a 37% reduction in diabetic patients.

Activation of the sympathetic nervous system also increases lipolysis and inhibits insulin release. The reduction in insulin further increases free fatty acids released from adipose tissue. The release of free fatty acids into plasma during acute myocardial infarction increases myocardial oxygen consumption and the ischaemic burden, which has been associated with increased infarct size and the occurrence of arrhythmic events.

Although it has been accepted for some time that high glucose levels during acute myocardial infarction among diabetics presage death and recurrent myocardial infarction, previous attempts to control hyperglycaemia in order to improve prognosis have been unsuccessful.

However, the recent DIGAMI study which studied intensified insulin treatment in patients with acute myocardial infarction and diabetes has changed the picture. Patients with either IDDM or NIDDM and onset of symptoms within 24 h were randomized to continuous insulin and glucose infusion followed by subcutaneous insulin treatment for 3 months or conventional care.

Although the incidence of reinfarctions, hospitalizations, development of non-fatal heart failure and need for coronary revascularization procedure were not different between the two groups, all fatal complications were significantly reduced in patients.
randomized to intensified insulin treatment after one year. Mortality was reduced from 26% in the control group to 19% in the infusion group, a reduction of 29% (P<0.03). The reduction of in-hospital mortality was 18%, but did not reach statistical significance. Surprisingly, the treatment effect was most pronounced in low risk patients without prior insulin treatment. Administration of glucose, insulin and potassium has been shown to reduce myocardial ischaemia\cite{19}, but this is the first time intensified insulin treatment has been shown to reduce mortality. In the present issue, the DIGAMI group\cite{20} present data on cause-specific one year mortality and morbidity. The most frequent cause of death was congestive heart failure which amounted to 66%. This contrasts with non-diabetic patients in whom sudden death is the major cause of post-myocardial mortality. However, cardiovascular mortality including congestive heart failure, fatal reinfarction, sudden death and stroke all tended to be decreased in patients with intensive insulin treatment, although the differences did not reach statistical significance. The similar effect on all modes of death may suggest a common mechanism.

Although the reduction in HbA1C was rather modest, 1.1% vs 0.42%, and glucose was reduced from 15.5 mmol l\(^{-1}\) to 8.2 and 9.0 mmol l\(^{-1}\), respectively, in the treated and control group, the DIGAMI trial is highly suggestive of improved metabolic control in the acute phase of myocardial infarction and in acute and long-term survival. Although the intensified insulin-glucose treatment only caused a modest additional effect on plasma glucose levels, it may have markedly improved cardiac utilization of glucose and reduction of free fatty acids. The study raises important questions about dosing, length of insulin administration, glucose target and mechanisms of action.

However, there may be a difference between NIDDM and IDDM with respect to long-term treatment effects. Hyperinsulinaemia is a possible risk factor for cardiovascular disease in NIDDM, and insulin treatment has been associated with extensive atherosclerotic changes compared to non-insulin treated diabetics\cite{21}. Intensive insulin treatment has been found to stimulate cholesterol synthesis and cause an over-production of cholesterol and reduction of HDL cholesterol levels\cite{22}.

A long-term trial is therefore warranted in order to evaluate the full benefit of short- and long-term insulin administration to NIDDM and IDDM patients with coronary heart disease, as an adjunct to the documented effect of beta-blockade and lipid lowering treatment.

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References

Determinants of the acute phase response in acute myocardial infarction

See page 1345 for the article to which this Editorial refers

It is well established that in patients with acute myocardial infarction the extent of necrosis is the main, but not the only, determinant of prognosis. Neither early ventricular fibrillation, age-related mortality nor the appearance of cardiac failure are necessarily related to infarct size. The reason for this variable cardiac response to the necrotic insult are probably multiple and require a clear understanding as they may represent independent, additional, determinants of prognosis. In this issue, Pietilä et al. report a significant association between mortality 6 months after an acute myocardial infarction and peak levels of serum C-reactive protein during the acute phase, in the absence of a significant association with infarct size estimated from peak levels of creatine kinase11. The observations of Pietilä et al. are intriguing and deserve some comment concerning the relationship of C-reactive protein with infarct size and prognosis.

Determinants of the acute phase response in acute myocardial infarction

Following acute myocardial infarction, blood levels of C-reactive protein reach a peak at about 48 h[2] which is closely correlated with infarct size in non-thrombolysed patients[3]. Smaller elevations were reported in patients with an open infarct-related artery than in those with a closed artery who also had a lower left ventricular ejection fraction (suggestive of a larger infarction)[4-5].

The rather weak correlation of peak C-reactive protein levels following acute myocardial infarction with enzymatic estimates of infarct size is not surprising as their accuracy is low, particularly when only peak values are considered following thrombolytic treatment (as was the case in the study reported in this issue[1]). Thus, left ventricular ejection fraction, or better, end-systolic volume, could represent a more reliable estimate of infarct size in patients who had a normal ventricular function before the myocardial infarction. However, the poor correlation between estimated infarct size and C-reactive protein elevation can result not only from inaccurate quantitation of myocardial necrosis, but also from a variable intensity of the individual acute phase response to inflammatory stimuli, in this case the extent of myocardial necrosis. This possibility is suggested by the observation that peak C-reactive protein levels in acute myocardial infarction are much higher in patients with elevated C-reactive protein values on admission (before any detectable enzymatic evidence of myocardial necrosis), although infarct size was similar[6]. It is also supported by the observation that, following coronary angioplasty, C-reactive protein values increase only in patients with basal elevation of C-reactive protein, and that the increase occurs in response to a greater production of interleukin-6[7]. If the intensity of the acute phase response was not necessarily proportional to the intensity of the inflammatory stimulus the variable C-reactive protein elevation in acute myocardial infarction may not only represent a consequence of the variable success of thrombolysis and of late recanalization or persistent occlusion of the infarct-related artery. Thus, the prognostic significance of peak C-reactive protein values may be partly (or in some patients) related to the extent of necrosis and partly (or in other patients) to the unknown individual determinants of the intensity of the acute phase response.

If the importance of a variable individual acute phase response in acute myocardial infarction is confirmed, its cause deserves further investigation.