Managing cardiovascular risk in patients with diabetes

Lars Rydén

The prevalence of diabetes is increasing dramatically. If the number of patients in the developed and developing worlds with diabetes is combined, there are currently 100 million. It is predicted that this will increase to 200–225 million within the next 25 years.[1]

There are a number of reasons for this dramatic increase. The aging of the general population is a significant factor. Also, lack of physical exercise combined with an unhealthy diet plays an important role. As developing countries continue to adopt the bad habits of the West, the incidence of diabetes will rise.

About 90% of diabetic patients will have type 2 diabetes, which develops with age and has a strong relation to macrovascular complications.

Patient outcome

It is interesting to observe the changing patterns of mortality and morbidity in diabetic and non-diabetic patients. For non-diabetic patients there has been a successive decrease in mortality caused by cardiovascular events.[2] However, in the diabetic population this has not been the case. For male diabetic patients there has been no significant change. In female diabetic patients the outcome has worsened over the years.

One reason for the poor outcome for diabetic patients is probably the divided care they receive. They are generally cared for by endocrinologists, although the main manifestations of their disease are cardiovascular which are treated by cardiologists. It is therefore important for endocrinologists and cardiologists to meet to plan patients' treatment protocols.

The risk of cardiovascular disease in the diabetic population is high. For example, the MRFIT trial showed that increasing blood pressure or cholesterol concentrations increases the risk for cardiovascular events in both diabetic and non-diabetic patients.[3] However, at each point the risk is much greater for diabetic patients.

Karolinska Hospital, Department of Cardiology, Thoracic Clinic 5 tr, S-171 76 Stockholm, Sweden

Correspondence to:
Professor Rydén
email: lars.ryden@ks.se

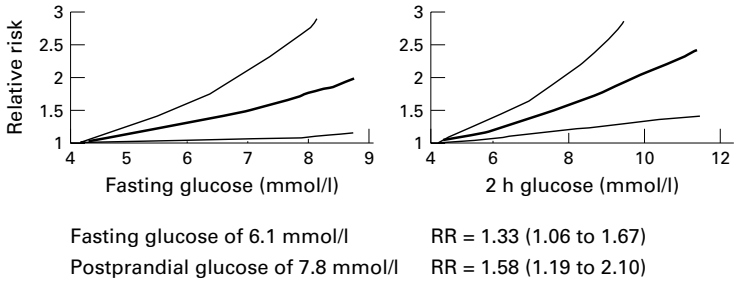

Figure 1 Results of a meta-analysis looking at glucose as a risk factor for cardiovascular morbidity and mortality. Reproduced with permission from Coutinho et al.[4] Copyright © 1999 American Diabetes Association.

Risk factors in diabetic patients

In non-insulin dependent diabetic patients the conventional risk factors for cardiovascular disease are common. For example, approximately 70% of patients will have hypertension. However, these cannot fully explain the high mortality rates. There must be other risk factors involved.

GLUCOSE

Glucose may be an independent risk factor for cardiovascular disease. A recent meta-analysis of almost 96 000 patients in 20 studies, with a follow up of 12.4 years and fasting and postprandial blood glucose measurements,[4] found that there was a successive and continuous increase in the relative risk of cardiovascular mortality with increasing blood glucose concentrations (fig 1). This was true at even low concentrations of blood glucose. A fasting blood glucose of 6.1 mmol/l, which represents borderline diabetes, resulted in a 33% higher risk for subsequent cardiovascular morbidity and mortality. With a postprandial blood glucose concentration of 7.8 mmol/l, the risk is increased by 58%.

This is supported by a recent study that looked at the risk of death in diabetic and non-diabetic patients with and without previous myocardial infarction (MI).[5] The patients were age and sex matched and followed for eight years. The worst outcome was for patients with diabetes and a previous MI.

Interestingly, the outcome for a diabetic patient without a previous MI was the same as that for a non-diabetic patient with MI. No one would doubt the need for a patient who has had an MI to have an aggressive secondary prevention programme, but it is equally important that the diabetic patient, even without a previous MI, receives adequate treatment.

The findings of this study are confirmed by unpublished data from the OASIS group.[6] This group compared diabetic and non-diabetic patients with and without unstable coronary artery disease (CAD). As expected the highest mortality was in the diabetic patients with unstable CAD. The lowest mortality was in the non-diabetic without previous manifestations of CAD. Diabetics with unstable CAD had the same outcome as non-diabetic patients without evidence of unstable CAD.

BLOOD PRESSURE

In type 1 diabetes, hypertension is usually related to nephropathy. In type 2 diabetes, however, hypertension is part of the metabolic syndrome. Therefore the vast majority of patients with type 2 diabetes have hypertension which increases the risk of cardiovascular disease.

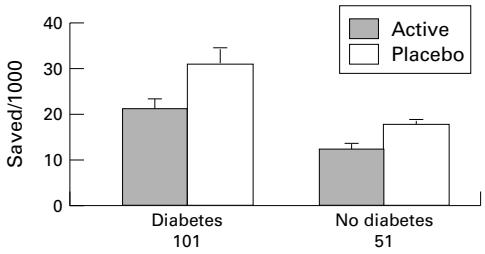

Figure 2 The efficacy of antihypertensive treatment in the diabetic patient: results from SHEP (major cardiovascular events over five years). Adapted from Curb et al.[7]

SHEP

One of the first studies to address the effect of antihypertensive treatment in diabetics was SHEP.[7] Four thousand non-diabetic patients and 583 patients with type 2 diabetes were randomised to either the diuretic chlorthalidone with atenolol or reserpine; or placebo with any other prescription. The study found that if 1000 patients were treated, 101 diabetics would be saved from an outcome but only 51 non-diabetics would avoid a cardiac event. This demonstrates that, the higher the risk, the efficacy of treatment is increased (fig 2).

HOT

A similar study looked at the incidence of cardiovascular events in 18 790 patients, 1501 of whom had diabetes.[8] All patients received treatment with felodipine combined with either an angiotensin converting enzyme (ACE) inhibitor or a β blocker. There were three target blood pressures: ⩽ 90 mm Hg; ⩽ 85 mm Hg; and ⩽ 80 mm Hg. The follow up was almost four years.

In the diabetic patients there was a considerable and significant reduction in risk of major cardiovascular events with lowering of blood pressure. It is therefore important that diabetic patients are treated aggressively.

UKPDS

This finding is supported by the results of the UKPDS study.[9] In this study patients with type 2 diabetes were treated with either tight or less tight blood pressure control. There was a significant 32% ($p = 0.019$) reduction in risk of cardiovascular events in patients treated with tight blood pressure control.

UKPDS also addressed the question of whether ACE inhibitors or β blockers have any specific advantages or disadvantages in this population. It found that compared to less well controlled blood pressure, there is actually no difference whether tight blood pressure control was achieved using an ACE inhibitor or a β blocker.

These three studies (SHEP, HOT, and UKPDS) confirm that hypertension in the diabetic should be treated aggressively. The goal blood pressure is ⩽135 mm Hg. To reach this target blood pressure a combination of drugs will usually be required.

LIPIDS

Dyslipidaemia constitutes a further important risk factor for cardiovascular disease, particularly in type 2 diabetes in which there is firm evidence of oxidative stress.

There is a difference in the lipid pattern between type 2 diabetics and non-diabetic subjects. Patients with type 2 diabetes are characterised by low concentrations of high density lipoprotein (HDL), a high concentration of triglycerides, and a lower rate of raised low density lipoprotein (LDL).

As cholesterol concentrations rise, there is a substantial and higher risk in the diabetic than in the non-diabetic population.[10] Control of blood cholesterol and blood lipids is therefore very important in the diabetic patient.

There are three studies which provide evidence for the effectiveness of lipid lowering treatments in diabetic patients: 4S, CARE, and LIPID.[11–13] However, these studies are not characteristic for the diabetic population and must therefore be interpreted with caution. For example, 4S had relatively few diabetic patients, who were characterised by high blood cholesterol and not very high triglycerides which is not typical for diabetic patients. CARE and LIPID are more characteristic but not completely so.

4S

In the 4S study the worst outcome in terms of cardiac events was for diabetic patients who did not receive lipid lowering treatment with simvastatin. The best outcome was for non-diabetics who received treatment. Diabetics and non-diabetics who received treatment had the same prognosis.[11]

CARE

Diabetics had a much higher incidence of cardiac events in the CARE study. It took two or three years to achieve a significant effect in these patients with pravastatin treatment. It is therefore important that some other form of treatment is started while waiting for the beneficial effects of lipid lowering.[12]

LIPID

In the LIPID trial there was a 19% decrease in heart disease mortality and non-fatal myocardial infarctions in diabetics which was not significant compared to the 25% reduction in the non-diabetic group.[13]

A meta-analysis of the results from these three trials shows a benefit of lipid lowering in diabetic patients. However, there is a need for additional studies using more typical diabetic patients.

The new recommendation for lipid lowering from the Swedish Medical Product Agency is total cholesterol < 5 mmol/l and LDL cholesterol < 3.0 mmol/l.

GLUCOSE

Interest has recently focused on whether the impact of blood glucose concentrations on cardiovascular risk can be reversed.

UKPDS

In the UKPDS study, intensive metabolic control using a variety of agents resulted in a 16% reduction in the number of new onset myocardial infarctions (this almost reached signifi-

Trial acronyms
4S: Scandinavian Simvastatin Survival Study
CARE: Cholesterol and Recurrent Events
DIGAMI: Diabetes and Insulin-Glucose infusion in Acute Myocardial Infarction
HOPE: Heart Outcomes Prevention Evaluation
HOT: Hypertension Optimal Treatment
LIPID: Long-term Intervention with Pravastatin in Ischaemic Disease
MRFIT: Multiple Risk Factor Intervention Trial
OASIS: Organization to Assess Strategies for Ischemic Syndromes
SHEP: Systolic Hypertension in the Elderly Programme
UKPDS: United Kingdom Prospective Diabetes Study

cance, p = 0.052).[14] The reason this result was not significant may be because the patients were at relatively low risk—young, without previous disease, and at the early stage of their disease. The 16% reduction in myocardial infarction translates into the prevention of one myocardial infarction if tight metabolic control is achieved in 46 patients. This analysis can be extended to show that each per cent reduction in HbA1c will result in an 18% reduction in myocardial infarction, which is very significant (p < 0.0001).

DIGAMI

The DIGAMI study was a secondary prevention study looking at the impact of good metabolic control in post-MI diabetic patients.[15] Patients were either treated rapidly with an infusion to achieve tight metabolic control or treated in any other way. Over a period of 3.4 years there was an overall reduction in mortality of 11% with good metabolic control which was significant (p = 0.011).

HOPE

The recently completed HOPE trial provides further evidence for the need to prescribe ACE inhibitors to diabetic patients. The study included many patients with diabetes and one risk factor for cardiovascular disease who received either 10 mg ramipril or placebo.[16]

Treatment with ramipril in diabetic patients reduced the primary outcome (stroke, myocardial infarction, and cardiovascular death) from 19.8% to 15.3% which was highly significant (p = 0.0004).[17] Moreover, in the general population of the HOPE study there was a reduction in new onset diabetes from 5.4% in the placebo group to 3.6% in the treatment group (p < 0.001).[16]

Conclusion

A diabetic patient is at as high a risk for a cardiac event as a patient who has suffered a myocardial infarction. There are a number of measures that can help these patients including antihypertensive treatment, lipid lowering treatment, good metabolic control, and also the possibility of preventing the appearance of new onset diabetes. It is therefore important that there is more widespread application of the evidence from clinical trials when treating diabetic patients.

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