

# Reducing the risks in diabetes

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### Abstract

Diabetes mellitus is an important risk factor for future cardiovascular events. To prevent cardiovascular disease, lifestyle modification is the first-line approach to the management of type 2 diabetes and metabolic syndrome, whereas strict glycaemic control is the first objective in type 1 diabetes. However, aggressive treatment to control atherogenic dyslipidemia, increased blood pressure, and hyperglycemia is needed when non pharmacologic approaches alone are ineffective or insufficient.

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### Introduction

Diabetes mellitus is a major health problem that affects more than 135 million people worldwide and is an important risk for future cardiovascular events in patients with or without ischemic heart disease [1]. Diabetic patients without overt coronary artery disease have a prognosis similar to that of non diabetic patients with coronary disease, whereas the cardiovascular death rate for diabetic patients with coronary disease is double that for those who are not diabetic [2]. Moreover, diabetes worsens outcomes in acute coronary syndromes, with a 5-year mortality of at least 50%. Thus patients with diabetes are prime candidates for primary or secondary prevention. The absolute risk of cardiovascular disease (CVD) in patients with type 1 (insulin-dependent) diabetes mellitus is lower than that in patients with type 2 (non insulin-independent) diabetes mellitus, in part because of their younger age and the lower prevalence of CVD risk factors, and in part because of the different pathophysiology of the two diseases. However, the relative risk of CVD in patients with type 1 diabetes compared with that of non diabetic individuals of similar age is dramatically increased in men and women. Furthermore, there are no data to suggest that the interventions documented to be of benefit in reducing CVD are less effective in patients with type 1 diabetes than in type 2 diabetes.

### Risk factors

In patients without symptoms, intervention to prevent CVD is based on risk assessment. Cardiovascular risk factors have additive, or even multiplicative, effects on mortality, such that each should be addressed whenever it is possible.

### Glycemic control

Although several clinical trials have shown a direct correlation between strict glycaemic control and reduction of microvascular disease, the relationship between strict glycaemic control and the reduction of macrovascular events has been less clear [3]. The UK Prospective Diabetes Study (UKPDS) found only borderline association between glucose control and the risk of myocardial infarction, with a marginal 16% reduction of risk after intensive hypoglycaemic treatment compared with conventional treatment.

Drugs used for intensive treatment mainly influence fasting glucose concentrations, but not postprandial changes in glucose concentration [4]. The recent guidelines from the European Society of Cardiology and the European Association for the Study of Diabetes suggest that an improvement in control of postprandial glycemia may decrease cardiovascular risk and mortality [5]. The Diabetes Control and

Complications Trial (DCCT) has clearly shown that, in patients with type 1 diabetes, improved glycaemic control translates into substantial reductions in macrovascular risk; in particular, improved glycaemic control was particularly beneficial in younger patients with a shorter duration of diabetes [6]. A recent meta-analysis demonstrated that improved glycaemic control led to substantial reductions in macrovascular risk in type 1 diabetes, but produced a smaller reduction in patients with type 2 diabetes [7]. The American Heart Association–American Diabetes Association recommendations for glycaemic control are summarized in *Table 1* [8]. It is important to underline that the only interventions that have been shown to be effective in reducing cardiovascular events in patients with diabetes mellitus are insulin in patients with acute coronary syndromes, and metformin and acarbose in primary and secondary prevention.

### Dyslipidemia

Although total and high-density lipoprotein (HDL) cholesterol concentrations in patients with type 2 diabetes are similar to those in individuals without diabetes, diabetic patients tend to have greater concentrations of both triglycerides and small dense low-density lipoprotein (LDL). Several studies have clearly demonstrated that even a moderate reduction in LDL cholesterol in individuals with type 2 diabetes results in a substantial reduction of cardiovascular events, and that this risk reduction is independent of baseline lipid concentrations or co-medication. Observational data from the UKPDS demonstrated that an increase of 1 mmol/L (38.5 mg/dL) in LDL cholesterol was associated with a 57% increase in CVD, and that an increase of 1 mmol/L (4 mg/dL) in HDL cholesterol was associated with a decrease in CVD endpoint [9,10].

For primary prevention, the guidelines of the American Diabetes Association suggest that, in diabetic patients with a total cholesterol >3.5 mmol/L (>135 mg/dL), statin therapy is recommended to achieve a reduction in LDL of 30–40%, regardless of baseline LDL concentrations [8]. Evidence is lacking for a role of statin therapy for primary prevention in individuals with type 1 diabetes.

An independent relationship between increased plasma triglycerides and vascular risk remains controversial, and guidelines are less specific with regard to the goals for HDL cholesterol and triglycerides (*Table 1*). Data from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study showed that, in primary prevention, fenofibrate is effective in reducing cardiovascular events, and that this drug can be safely used in combination with statins for the treatment of diabetic dyslipidemia [11].

### Hypertension

Arterial hypertension is a common comorbidity in diabetic patients. The Multiple Risk Factor Intervention Trial (MRFIT) and the PROspective Cardiovascular Munster (PROCAM) study have shown that arterial hypertension carries a greater cardiovascular risk in patients with diabetes than in non diabetic individuals [10,12]. Furthermore, the association of hypertension and diabetes is a much greater risk factor for cardiovascular events in women than in men (relative risk 4.6 compared with 2.4, respectively). The UKPDS and the Hypertension Optimal Treatment (HOT) trial have demonstrated that decreasing the blood pressure reduces the risk of cardiovascular events [13,14]. The European Society of Cardiology–European Association for the Study of Diabetes guidelines recommend lower blood pressure targets in patients with diabetes (<130/80 mm Hg) than in those without diabetes, and suggest, as the initial strategy, blockade of the renin–angiotensin–aldosterone system, especially in those patients at high cardiovascular risk [5].

### Body weight and fat distribution

Most individuals with type 2 diabetes are overweight, and obesity worsens the metabolic and physiologic abnormalities associated with diabetes. Obesity, and in particular visceral obesity, per se, is a significant cardiovascular risk. Intra-abdominal or visceral adipose tissue has been proposed as the major site of fat deposition associated with the adverse metabolic consequences of obesity. It is believed that abdominal adiposity is the initial event that results in insulin resistance, by an increase in free fatty acid flux in the portal and systemic circulations. Intra-abdominal adipose tissue may also contribute to other mechanisms of increased atherosclerotic risk, including inflammatory, prothrombotic, and fibrinolytic factors.

Several studies have shown that weight loss is associated with a significant decrease in total and LDL cholesterol, triglycerides, and blood pressure, in addition to improved glycaemic control, and is consequently associated with a significant reduction in morbidity and mortality for cardiovascular and other disease [15,16].

For type 1 diabetes, intensive insulin treatment results in weight gain. The Diabetes Control and Complications Trial showed that patients allocated randomly to intensive insulin therapy had greater weight gain than those receiving conventional insulin therapy. Despite this weight gain, improved glycaemic control with intensive insulin therapy resulted in improvements in lipid concentrations and reduced the atherogenicity of the lipoprotein profile. In contrast to individuals without diabetes, in patients with

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Table I. From American Heart Association (AHA)–American Diabetes Association (ADA) recommendations [8] for the primary prevention of cardiovascular disease in people with diabetes.

### Lifestyle management

#### Weight

Lifestyle changes: increased regular physical activity can produce long-term weight loss of the order of 5–7% of starting weight, with improvement in blood pressure.

#### Medical nutrition therapy

Fats: Total dietary fat intake should be moderated (25–35% of total calories). Saturated fats:  $\leq 7\%$  of energy intake, cholesterol  $\leq 200$  mg/day. *Trans*-unsaturated fatty acids:  $\leq 1\%$  of energy intake.

Alcohol: 1 drink (a 354 mL [12-oz] beer, a 118 mL [4-oz] glass of wine) for adult women and 2 drinks for adult men. Sodium intake 1200–2300 mg/day.

#### Physical activity

150 minutes of moderate-intensity aerobic physical activity or 90 minutes of vigorous aerobic exercise per week is recommended, and should be distributed over at least 3 days per week, with no more than two consecutive days without physical activity.

#### Blood pressure

SBP  $\leq 130$  mm Hg or DBP  $\leq 80$  mm Hg.

SBP 130–139 mm Hg or DBP 80–89 mm Hg should initiate lifestyle modification alone for a maximum of 3 months. If, after these efforts, targets are not achieved, treatment with pharmacological agents should be initiated.

Patients with a BP  $\geq 140/90$  mm Hg should receive drug therapy that includes either an ACE inhibitor or an ARB + lifestyle and behavioral therapy.

#### Lipids

LDL cholesterol  $\leq 2.6$  mmol/L ( $\leq 100$  mg/dL), HDL cholesterol  $\geq 1.3$  mmol/L ( $\geq 50$  mg/dL), triglycerides  $\leq 1.7$  mmol/L ( $\leq 150$  mg/dL)

Statin therapy should be initiated on the basis of risk factor assessment and clinical judgment.

The AHA suggests that, in patients with triglyceride concentrations of 2.26–5.7 mmol/L (200–499 mg/dL), a non HDL cholesterol goal of 3.36 mmol/L (130 mg/dL) is a secondary target.

If triglycerides are  $\geq 5.7$  mmol/L ( $\geq 500$  mg/dL), therapeutic options include fibrate or niacin before LDL-decreasing therapy and treatment of LDL cholesterol to goal after triglyceride-decreasing therapy. A non HDL cholesterol concentration  $\leq 3.36$  mmol/L ( $\leq 130$  mg/dL) should be achieved if possible.

The ADA suggests decreasing triglycerides to  $\leq 1.7$  mmol/L ( $\leq 150$  mg/d) and increasing HDL cholesterol to 1.15 mmol/L ( $>40$  mg/dL).

In women, HDL goal  $\geq 1.7$  mmol/L ( $\geq 50$  mg/dL) should be considered.

#### Tobacco

Every tobacco user should be advised to quit.

#### Antiplatelet agents

Aspirin therapy (75–162 mg/day) should be recommended as a primary prevention strategy in those with diabetes at increased cardiovascular risk, including those who are  $\geq 40$  years of age or who have additional risk factors (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria).

#### Glycemic control

The HbA<sub>1c</sub> goal for patients in general is  $\leq 7\%$ .

The HbA<sub>1c</sub> goal for the individual patient is close to the normal ( $\leq 6\%$ ) as possible, without causing significant hypoglycemia.

Table I. continued.

#### NIDDM

At the present time, all the recommendations listed above for patients with NIDDM appear to be appropriate for those with IDDM as well.

ACE, angiotensin-converting enzyme; ARB, angiotensin II type 1 receptor blocking agent; BP, blood pressure; CVD, cardiovascular disease; HbA<sub>1c</sub>, glycated hemoglobin; HDL, high-density lipoprotein; IDDM, type 1 diabetes mellitus; LDL, low-density lipoprotein; NIDDM, type 2 diabetes mellitus; SBP, DBP, systolic and diastolic blood pressures.

type 1 diabetes there is no association between insulin resistance and abdominal adiposity [6].

### Physical exercise

Exercise contributes to the control of risk factors. Evidence of its efficacy has led to the conclusion that a sedentary lifestyle is a strong single risk factor for CVD. Aerobic training improves glycemic control, but a dose–effect relationship has not been shown. Training is associated with a reduced risk of hypoglycemia and a decrease in postprandial hyperglycemia in type 2 diabetes. A meta-analysis by Sigal et al [17] revealed that physical exercise leads to a decrease in glycated hemoglobin (HbA<sub>1c</sub>) that is large enough to achieve a significant reduction in the frequency of the degenerative complications associated with type 2 diabetes. Training slows the evolution of atherosclerotic disease in individuals with type 2 diabetes, leading to decreased cardiovascular morbidity and mortality independent of other risk factors, namely overweight, smoking, hypertension, and dyslipidemia. Several studies have shown that greater physical activity is associated with a lower mortality among patients with type 1 diabetes, but there is no convincing evidence that physical activity has a positive effect on glycemic control in type 1 diabetes [18].

### Metabolic syndrome

The metabolic syndrome is a cluster of metabolic disorders in which insulin resistance is combined with one or more of the following features: obesity, type 2 diabetes, essential hypertension, hypertriglyceridemia, low HDL cholesterol. Several studies on the association of the metabolic syndrome and risk of CVD have been published.

A recent meta-analysis [19] showed that the metabolic syndrome as defined by the World Health Organization or Adult Treatment Panel III is associated with an increase risk of all-cause and CVD

mortality and increased incidence of CVD, even among populations initially free of diabetes and CVD. In particular, the relative risk for CVD associated with metabolic syndrome was greater in women than in men, and greater in studies in which the World Health Organization definition was used. Another recent meta-analysis confirmed these data and demonstrated that metabolic syndrome increases cardiovascular risk, and that cardiovascular risk conferred by metabolic syndrome is 3-fold greater in women than in men [20].

Several studies have demonstrated that lifestyle modification is the first-line treatment for obesity and its metabolic sequelae [21,22]. Treatment of individual components aims at controlling atherogenic dyslipidemia, increased blood pressure, and hyperglycemia when non pharmacologic approaches alone are ineffective or insufficient [22–24].

Primary care physicians have a critical role in the early identification and treatment of patients who are at increased risk for the development of type 2 diabetes and CVD because of their obesity and associated complications.

### Antiplatelet agents

Patients with diabetes have an increased risk of atherothrombosis, therefore antiplatelet therapy is indicated as first-line preventative strategy in type 2 diabetes [25]. Several studies have shown that aspirin reduces the risk of major cardiovascular events by about 25% in diabetic patients, and the American Diabetes Association recommends low-dose aspirin therapy for primary prevention in diabetic patients from age 40 years (Table 1).

### Conclusion

Diabetes mellitus is an important risk for CVD. Lifestyle interventions are effective in the prevention of CVD events in patients with diabetes; however, pharmacologic treatment is often necessary. Cardiovascular preventative strategies should not be focused on glucose control therapy alone, but must include treatment of lipid profile and blood pressure. Therefore, in order to reduce cardiovascular risk, an aggressive management of lipids and blood pressure with pharmacologic treatment, together with lifestyle changes, must be implemented in all diabetic patients. ■

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