Cardiovascular Risk Factors and Complications in Type 1 and Type 2 Diabetes

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ABSTRACT

Patients with diabetes have increased risk of cardiovascular disease (CVD) and mortality compared to the general population. The aim of this work was to describe the clinical characteristics and risk factors in patients with type 1 diabetes, and also to investigate the association between glycaemic control and CVD in type 1 and type 2 diabetes, and to analyse the association between BMI, overweight and obesity, and CVD in type 2 diabetes.

These observational studies comprise patients from the Swedish National Diabetes Register (NDR). Clinical characteristics and risk factor control in type 1 diabetes were analysed in two cross-sectional samples, in 1997 and 2004. 7454 patients with type 1 diabetes were followed from 2002/03 to 2007, and 13,087 patients (Study III) and 18,336 (Study IV) with type 2 diabetes were followed from 1997/98 to 2003, regarding fatal/non-fatal CVD events. Cox proportional hazard models were used to estimate adjusted hazard ratios with 95% confidence intervals and to estimate 5- and 6-year event rates for the outcomes.

In patients with type 1 diabetes slight but significant improvements were seen in glycaemic control, blood pressure and lipid levels from 1997 to 2004. Hazard ratios for coronary heart disease (CHD) and CVD per 1%-unit increase in baseline HbA1c were 1.31 and 1.26 (p<0.001), respectively, when adjusted for age, sex, duration of diabetes and cardiovascular risk factors. Adjusted 5-year event rates of CHD and CVD increased progressively with higher HbA1c levels. Patients with HbA1c levels of 5-7.9% (mean 7.2%) at baseline had about 40% lower risk for CHD and CVD, compared with patients with HbA1c 8-11.9% (mean 9.0%). In type 2 diabetes adjusted hazard ratios for a 5-unit increase in BMI were 1.15 for first-incident CHD and 1.13 for CVD. Obesity was associated with a 44% increase in risk of CVD, and overweight with a 24% increase in risk, compared with normal weight. Adjusted hazard ratios for a 1%-unit increase in HbA1c were 1.11 for CHD and 1.10 for CVD (p<0.001), and the corresponding adjusted 6-year event rates for these outcomes increased progressively with higher baseline and updated mean HbA1c values, also when sub-grouping the data by duration, previous CVD or hypoglycaemic treatment. A group of patients with a mean baseline HbA1c of 6.5% showed a 20% lower risk of CHD and a 16% lower risk of CVD, than a group with a mean HbA1c of 7.5%.

These large observational studies on patients with diabetes in everyday clinical practice show a slow improvement in glycaemic control and risk factors in type 1 diabetes. Higher HbA1c level was found to be independently associated with increased risk of CHD and CVD, emphasizing the role of HbA1c as a strong independent risk factor in type 1 diabetes. In type 2 diabetes, increasing risks of CHD and CVD were seen in patients with higher HbA1c levels, while no risk increase was seen in those with low HbA1c levels. HbA1c levels lower than 7% were associated with a lower risk of CVD, providing support for current treatment guidelines. Higher BMI, overweight and obesity independently increased the risk of CHD and CVD in patients with type 2 diabetes, providing additional evidence that overweight and obesity should be counteracted in type 2 diabetes.

LIST OF ORIGINAL STUDIES

This thesis is based on the following studies, which will be referred to in the text by their Roman numerals.

I   Eeg-Olofsson K, Cederholm J, Nilsson PM, Gudbjornsdottir S, Eliasson B. Glycemic and risk factor control in type 1 diabetes: results from 13,612 patients in a national diabetes register. Diabetes Care. 2007;30(3):496-502. Copyright © 2007, American Diabetes Association.

II   Eeg-Olofsson K, Cederholm J, Nilsson PM, Zethelius B, Svensson AM, Gudbjornsdottir S, Eliasson B. Glycemic control and cardiovascular disease in 7,454 patients with type 1 diabetes: an observational study from the Swedish National Diabetes Register (NDR). Diabetes Care. 2010;33(7):1640-1646. Copyright © 2010, American Diabetes Association.

III   Eeg-Olofsson K, Cederholm J, Nilsson PM, Zethelius B, Nunez L, Gudbjornsdottir S, Eliasson B. Risk of cardiovascular disease and mortality in overweight and obese patients with type 2 diabetes: an observational study in 13,087 patients. Diabetologia. 2009;52(1):65-73. Copyright © 2008, Springer-Verlag.

IV   Eeg-Olofsson K, Cederholm J, Nilsson PM, Zethelius B, Svensson AM, Gudbjornsdottir S, Eliasson B. New aspects of HbA1c as a risk factor for cardiovascular diseases in type 2 diabetes: an observational study from the Swedish National Diabetes Register (NDR). J Intern Med. 2010. Article first published online: 21 July 2010. Copyright © 2010, John Wiley and Sons.

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LIST OF ABBREVIATIONS

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADA	American Diabetes Association
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
BMI	Body mass index
CHD	Coronary heart disease
CHF	Congestive heart failure
CVD	Cardiovascular disease
DCCT	Diabetes Control and Complications Trial
Pittsburgh EDC	Pittsburgh Epidemiology of Diabetes Complications study
EDIC	Epidemiology of Diabetes Interventions and Complications study
EURODIAB PCS	European Diabetes Prospective Complications Study
HbA1c	Heamoglobin A1c
HR	Hazard Ratio
ICD	International Classification of Diseases
LADA	Latent autoimmune diabetes of the adult
MI	Myocardial infarction
NDR	National Diabetes Register
NHANES	National Health and Nutrition Examination Survey
OHA	Oral hypoglycaemic agent
RCT	Randomized controlled trial
UK GPRD	United Kingdom General Practice Research Database
UKPDS	United Kingdom Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial
WHO	World Health Organization
WHR	Waist:hip ratio

CONTENTS

PREFACE

This thesis is based on data from the National Diabetes Register (NDR) in Sweden, a nationwide register of quality control. The aim of the NDR is to improve diabetes care and to ultimately promote health in patients with diabetes. To improve the quality of care it is necessary to first observe which measures are taken and which are not, and then identify the differences to establish how health outcomes are affected. Examples of health outcomes are retinopathy, blindness, cardiovascular disease and mortality, but self-perceived health and well-being are also included in health outcomes. New information and knowledge must be communicated to healthcare providers and patients to ensure evidence-based and consistent care. The overall goal of the work presented in this thesis is to contribute to improving the quality of diabetes care, for the benefit of the individual patient.

INTRODUCTION

DIABETES MELLITUS

Diabetes mellitus is a chronic illness of multiple aetiology, characterized by hyperglycaemia as a result of insufficient insulin secretion or impaired insulin action, or both (1). Based on the aetiology and clinical presentation, diabetes is classified as type 1 diabetes, type 2 diabetes, gestational diabetes or other specific forms. Diabetes is associated with specific long-term microvascular complications, including retinopathy, nephropathy and neuropathy, and macrovascular damage, resulting in coronary heart disease, stroke and peripheral vascular disease (2, 3). The World Health Organization (WHO) criteria for the diagnosis of diabetes are two consecutive values of fasting plasma glucose ≥7.0 mmol/L, or a 2-hour plasma glucose value after a 75 g oral glucose tolerance test of ≥11.1 mmol/L (2). The diagnostic level of fasting plasma glucose was lowered from 7.8 mmol/L to ≥7.0 in 1998 to better identify those with increased risk of microvascular and macrovascular complications, as premature mortality had been recorded in patients with blood glucose levels below 7.8 mmol/L (1, 2).

Type 1 diabetes is an autoimmune, inflammatory disease in which the insulin-producing beta cells of the pancreas are destroyed, leading to complete insulin deficiency and hyperglycaemia in genetically susceptible individuals. Environmental trigger mechanisms are believed to be involved, but these are not fully understood. Most patients develop the disease at a young age, but it can occur at any time of life (4, 5). The main pathophysiological features of type 2 diabetes include pancreatic beta cell failure, leading to insufficient insulin secretion, and increased insulin resistance in the liver, fat tissues and muscles. Insulin resistance enhanced by physical inactivity and obesity leads to increased output of glucose from the liver and decreased glucose uptake in skeletal muscles. The beta cells initially compensate for this by increased insulin secretion, but the progression of beta cell failure leads to hyperglycaemia and eventually type 2 diabetes. Genetic factors contribute to both insulin insensitivity and beta cell failure. The onset of type 2 diabetes is often slow, and symptoms can initially be discrete leading to delayed diagnosis (6, 7).

The epidemiology of diabetes

It has been estimated that the global prevalence of diabetes in individuals of all ages will increase, from 2.8% in 2000, to 4.4%, in 2030, affecting 366 million people worldwide (8). Type 1 diabetes is usually estimated to account for 5-10% of all diabetes cases (4). The estimated prevalence of diabetes (including 1/3 undiagnosed type 2 diabetes) in England in 2001 was 4.4% (of which 7.7% was type 1 diabetes), with a marked increase in prevalence with age (0.3% 0-29 years, 3.4% 30-59 years and 13.9% ≥60 years) (9). In Ontario, Canada the age-adjusted prevalence of diabetes has increased from 5.2% in 1995, to 6.9% in 2000, and to 8.8% in 2005 as a result of both rising incidence and declining mortality (10). A study in Denmark reported that the prevalence had more than doubled between 1995 and 2007, from 1.9% to 4.2%, due to decreasing mortality rates and increasing incidence (11).

However, studies performed in Sweden have shown no increases in the incidence and small or no increase the prevalence of diabetes in subject since the late 1980s (12-16). In the study from northern Sweden there was no increase in the prevalence of diabetes in subjects 25-49 years old from 1986 to 1999 (12). Jansson and colleagues reported stable incidence and prevalence from

1988 to 2001 in the municipality of Laxå with age-adjusted prevalence of about 4.4% (13). The total prevalence in Skaraborg county was 3.2% in 1995 with an annual increase of 6% from 1991 to 1995 (14, 15). A study from Uppsala reported an increase in total prevalence of type 2 diabetes from 2.2% to 3.5% from 1996 to 2003 due to decreased mortality (16). In Sweden in 2009 there were approximately 365,000 patients with diabetes (17).

Incidence of type 1 diabetes
The incidence of the onset of type 1 diabetes in childhood (0-14 years) was studied in the WHO DIAMOND project, which extended from 1990 to 1999 (18). The age-adjusted incidence rates varied across the world; the highest incidence rate being found in Finland, 40 per 100,000/year and the lowest in Venezuela, 0.1 per 100,000/year. Sweden had the third highest incidence rate in the world (30 per 100,000/year) (18). A European report on childhood onset of type 1 diabetes reported an annual incidence rate increase of 3.9% from 1989-93 to 1999-2003 (19). However, a previous study from Sweden reported that incidence rates in the age group 0-34 years did not increase between 1983 and 1998, but shifted towards younger age at diagnosis (20). Thunander and colleagues investigated newly diagnosed cases of diabetes in the period 1998 to 2001 in Kronoberg county in Sweden and found an incidence of type 1 diabetes of 27 per 100,000/year in children and young adults <40 years, and 34 per 100,000/year in adults aged 40 to 100 years (21).

Obesity and overweight epidemiology
The increasing prevalence of type 2 diabetes is closely linked to the increase in overweight and obesity (22). The body mass index (BMI), calculated as the weight in kilograms divided by the height in metres squared, is a measure of general obesity, and the WHO definitions are: normal weight BMI <25 kg/m^2, overweight BMI 25-29.9 kg/m^2 and obesity BMI ≥30 kg/m^2 (23). The prevalence of obesity is increasing in the US and in 2001 was 21% (22). Although the prevalence is lower in Sweden, there has been an increase in obesity from 5% in the 1980s to 10% in 2002-03, and at that time the prevalence of overweight or obesity (BMI >25 kg/m2) was 44% and in 2008-09 was 46%, among those aged 16-84 years (24).

CARDIOVASCULAR DISEASE
Cardiovascular diseases are large-vessel diseases including coronary heart disease, stroke and peripheral vascular disease. Atherosclerosis, which is the major underlying cause of cardiovascular disease (CVD), is an ongoing inflammatory process in the vessel wall, leading to endothelium dysfunction and plaque formation (25). Acute manifestations of CVD are often related to plaque erosion or rupture triggering thrombosis (26). The atherosclerotic process is enhanced in diabetes due to factors related to chronic hyperglycaemia and insulin resistance, resulting in increased oxidative stress and increased inflammation and in endothelial dysfunction, as well as hypercoagulability and a more atherogenic lipid profile (27-30).

Cardiovascular disease epidemiology
In the Western world, standardized mortality rates have been halved over the past two decades, but CVD was still the most common cause of death in Sweden in 2008, accounting for approximately 40% of all deaths, in both men and women (17). Studies carried out in the UK, the US and Sweden have shown a 50% reduction in mortality due to coronary heart disease (CHD) over the past two decades, and half of this decline was explained by a reduction in

major cardiovascular risk factors such as smoking, cholesterol and blood pressure; however, this was counteracted by increases in BMI and prevalence of diabetes (31-33). The WHO MONICA project also reported that CHD mortality rates were declining, and that advances in medical care, including changes in coronary care and secondary prevention, were closely linked to this progress (34, 35).

Diabetes and cardiovascular disease

Patients with diabetes run a marked increase in the risk of cardiovascular disease and mortality, compared with the general population, with a 2-4-fold increase in type 2 diabetes (36-40), and 4-8-fold increase in type 1 diabetes (41, 42). A recent large meta-analysis of 102 prospective studies on 698,782 participants with no history of myocardial infarction or stroke, and 410,299 with diabetes (both type 1 and type 2) revealed about a 2-fold increase in the risk of CHD and stroke in patients with diabetes, being somewhat higher for coronary death than for non-fatal myocardial infarction (43). Two studies based on the General Practice Research Database (GPRD) in the UK including over 7000 type 1 diabetic patients showed a 4-fold increase in the risk of mortality compared with controls; the major cause of death being CVD (44), and a 4-8-fold increase in major CVD (45).

Comparison of data from the US National Health and Nutrition Examination Survey (NHANES) regarding three cohorts of adults, 35-74 years old from the 1970s, 1980s and 1990s, revealed decreasing rates of total and CVD mortality in men with diabetes, but not in women with diabetes, where both an increasing rate of total mortality and an unchanged rate of CVD mortality were seen (46). However, a population based study from Norway have shown improved CHD mortality rates in adults both with and without diabetes, but still two-fold higher risk in adults with than without diabetes (47). Results from Sweden also indicate declining mortality rates in both men and women with diabetes between 1980 and 2004 (48). Norhammar and colleagues studied one year mortality rates after an acute MI and reported improved survival rates from 1995 to 2002 from 29.7% to 19.7% in patients with diabetes and from 16.6% to 12.1% in patients without diabetes (49).

Haffner and colleagues showed in 1998 in a Finnish population study that patients with type 2 diabetes had the same risk of fatal and non-fatal myocardial infarction (MI) as patients with previous myocardial infarction, and that patients with both diabetes and prior MI had more than double that risk (50). After a total follow-up period of 18 years, patients with diabetes and no prior MI had the same risk of mortality due to CHD as patients with prior MI (51). This understanding has led to attention being focused on cardiovascular risk factors in patients with diabetes.

CARDIOVASCULAR RISK FACTORS

Cardiovascular risk factors such as hypertension, cholesterol level, smoking and diabetes have been acknowledged for many years (52). More recently, the INTERHEART study, a cross sectional study on myocardial infarction, with 15,152 cases and 14,820 controls, from 52 countries around the world, found that smoking, abnormal lipid levels, diabetes, hypertension, abdominal obesity and psychosocial factors increased the risk of MI, whereas the regular consumption of alcohol, fruit and vegetables, and physical activity lowered the risk (53). The authors concluded that, taken together, these nine modifiable risk factors could explain approximately 90% of the MI risk. Similarly, the recently published INTERSTROKE study showed that similar risk factors could account for 90% of the stroke risk (54). The association between overweight and obesity, and increased risk of CVD and mortality is well established in the general population, in both men and women (55-59).

Cardiovascular risk factors in diabetes

Most of the major CVD risk factors are the same in diabetes as in the general population (36, 52). Risk factors associated with CHD have been assessed in newly diagnosed patients with type 2 diabetes in an observational study of patients included in the United Kingdom Prospective Diabetes Study (UKPDS) (60). Briefly, the UKPDS, a landmark study in type 2 diabetes, recruited 3867 newly diagnosed patients with type 2 diabetes, aged 25-65 years, during 1977 to 1991, with the aim of establishing whether intensive glucose control could reduce the risks of micro- and macrovascular complications in type 2 diabetes (61). In 2693 patients, followed for mean of 7.9 years, higher levels of low-density lipoprotein (LDL) cholesterol, lower levels of high-density lipoprotein (HDL) cholesterol, higher blood pressure, smoking and hyperglycaemia at baseline were all associated with increased risk of CHD, whereas higher BMI and waist:hip ratio (WHR) were not (60). Although overweight and obesity are highly prevalent among patients with type 2 diabetes (9, 22, 62, 63), studies in patients with type 2 diabetes have reported inverse, no or positive correlation between increasing BMI and CVD and mortality (64-67). Furthermore, diabetes-specific microvascular complications also increase the risk of CHD (68).

CVD risk factors in type 1 diabetes differ to some extent from those in type 2 diabetes. Nephropathy, both micro- and macroalbuminuria, is a major independent risk factor for both CHD and mortality (69-72). In the 10-year follow-up of the Pittsburgh EDC study, 657 patients with type 1 diabetes diagnosed from 1950 to 1980 have, after baseline examination in 1986-88, been followed-up every other year regarding complications and risk factors, and it was found that nephropathy, hypertension, lipid levels, and smoking independently predicted CHD (73). The EURODIAB Prospective Complications Study (PCS) has reported risk factors for CHD and mortality in 2787 type 1 diabetes patients followed for 7 years, and found that age and albuminuria at baseline in both men and women, WHR in men, and systolic blood pressure in women, were independent risk factors for CHD (70), while macroalbuminuria, neuropathy, pulse pressure, non-HDL cholesterol and WHR were associated with increased risk of mortality (71). The original EURODIAB PCS involved 3250 patients with type 1 diabetes, aged 15-60 years, recruited from 31 centres in 16 European countries during 1989-1991, who have been followed prospectively. Interestingly, in neither the EURODIAB study nor in the Pittsburgh EDC study was glycaemia, measured as haemoglobin A1c (HbA1c) at baseline, independently associated with CHD or mortality.

Risk factor control in diabetes

Intervention studies on patients with diabetes have shown that treatment of hypertension, as well as treatment with angiotensin-converting enzyme inhibitors irrespective of blood pressure lowering effect, reduces the risk of both microvascular disease and CVD (74-76). The treatment of hyperlipidaemia, in both primary and secondary preventions, also lowers the risk of CVD (77-79). The benefit of multi-factorial risk factor control is shown in the Steno-2 study, comparing intensive multi-factorial treatment, aimed at both pharmacological treatment and lifestyle interventions with standard care in patients with type 2 diabetes and microalbuminuria (80, 81). Patients were followed for mean of 7.8 years, and intensively treated patients, with lower levels of HbA1c, blood pressure, cholesterol and microalbuminuria, showed a 50% reduction in both microvascular and macrovascular (absolute risk reduction of 20%) complications (80). After additional observational follow-up of 5.5 years (total 13.3 y), risk factor control between the groups levelled out, but there was still a 50% reduction in CVD risk and a 50% reduction in total mortality in the former, intensively treated group (81).

Glycaemic control

Glycaemic control is of great concern to both patients and healthcare professionals, and a great deal of effort is dedicated to this by those engaged in diabetes care (82-85). It is well established that intensive glycaemic control reduces the risk of microvascular complications in patients with type 1 diabetes (86, 87) and in type 2 diabetes (61, 88). However, the role of glycaemic control in reducing the risk of macrovascular complications is less clear.

Measurement of glycaemia in diabetes care

Haemoglobin A1c (HbA1c) is regarded as the gold standard for monitoring long-term glycaemic control, as it is clearly related to development of microvascular complications (89). Circulating plasma glucose binds non-enzymatically and irreversibly to the haemoglobin of the red blood cells, and the A1c fraction is directly related to the plasma glucose concentration. Since the red blood cells circulate for a period of about 120 days, HbA1c represents the mean glycaemic level over the past 2 to 3 months (89). It has been shown that HbA1c is well correlated to an average glucose level, where a 1% increase in HbA1c represents an increase in average plasma glucose of approximately 1.6 mmol/L (90). In Sweden, HbA1c is measured with the Mono-S technique, which gives values about 1% unit lower than the DCCT (Diabetes Control and Complications Trial) standard. The Mono-S HbA1c level can be converted to the DCCT standard using a formula (91). Consensus on the worldwide standardization of HbA1c measurements and a change in units from % to mmol/mol was achieved in 2007 (an HbA1c (DCCT) value of 5% corresponds to ~ 33 mmol/mol and 8% to ~ 65 mmol/mol) (92). The implementation process of this new standard started in Sweden September 2010.

Glycaemic control in type 1 diabetes

No long-term, randomized clinical trials have been performed on patients with type 1 diabetes adequately examining the relationship between glycaemic control and macrovascular complications, and epidemiological studies have shown conflicting results (70, 71, 93-98). The Diabetes Control and Complications Trial (DCCT), a landmark study of the effects of intensive glucose lowering therapy on development of microvascular complications carried out in the US in 1441 patients with type 1 diabetes, showed no significant reduction of CVD risk (86, 94). The following observational Epidemiology of Diabetes Interventions and Complications (EDIC) study, showed that patients who had previously been subjected to intensive glucose control

during the DCCT had a considerably lower risk of CVD than patients receiving standard treatment, in the period 1983-1993 (93). A small study conducted in Finland on late-onset type 1 diabetic patients without albuminuria showed an increased risk of CHD with poor glycaemic control (95), but the EURODIAB PCS, the Pittsburgh EDC and the Wisconsin Epidemiologic Study of Diabetic Retinopathy found no significant relationship between glycaemia and CHD after controlling for other cardiovascular risk factors (70, 71, 96, 97). However, a recent study by the Pittsburgh EDC showed that a change in HbA1c was related to CHD, whereas baseline HbA1c was not (98).

Glycaemic control in type 2 diabetes
Epidemiological studies in type 2 diabetes (60, 68, 99-101), as well as studies on mainly non-diabetic individuals (102-105), have shown a positive association between HbA1c and CVD risk, although recent, randomized clinical trials have not been able to confirm that intensive treatment and lowering of HbA1c were beneficial with regard to CVD risk (88, 106, 107). Two large multi-centre randomized trials including over 10,000 participants each, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), did not show that intensive glucose control reduced the cardiovascular risk or mortality (88, 106). In fact, the ACCORD study showed an increase in the risk of all-cause mortality in the intensively treated group, (HR 1.22 (95% confidence interval (CI)1.01-1.46; p=0.04), and the study was discontinued early after 3½ years (106). The comparison of two groups with median HbA1c levels of 6.4% and 7.5% in the ACCORD study showed no significant risk reduction in the primary outcome (non-fatal MI and stroke, and CVD mortality) with intensive glucose control after 3½ years (HR 0.90 (0.78-1.04); p=0.16), although a significant reduction was seen in the risk of non-fatal MI (HR 0.76 (0.62-0.92); p=0.004). The ADVANCE trial, comparing two groups with mean HbA1c levels of 6.5% and 7.3%, showed no significant reduction of risk for major macrovascular events after 5 years (HR 0.94 (0.84-1.04); p=0.32) or all-cause mortality (HR 0.93 (0.83-1.06); p=0.28) (88). Similar results were reported in the Veterans Affairs Diabetes Trial (VATD) trial, conducted in the US, i.e. no effect on the risk of CVD or total mortality as the result of intensive treatment (107).

These results, both the non-significant findings in the ADVANCE and VATD studies, and the increase in total mortality in the ACCORD study, have been extensively discussed (85). Although the study populations were large, they may still have been under¬powered to detect a difference with an overall expected incidence rate of CVD events of 2%. Perhaps the follow-up time was too short. Maybe the intensive treatment strategies were too aggressive in patients vulnerable to cardiovascular events. The debate intensified early in 2010, following the publication of the results of an observational study based on the UK GPRD, which showed an increased risk of all-cause mortality and progression to CVD in patients with lower and higher HbA1c levels, and the lowest risk at a level of 7.5%, in both patients treated with oral agents and in patients on insulin-based therapies (108).

GUIDELINES ON DIABETES CARE

National as well as international guidelines on diabetes care and on the prevention of cardiovascular diseases have been drawn up based on evidence-based knowledge and concensus, with the intention of improving care and the well-being and health of the individual diabetes patient (82, 83, 109). The American Diabetes Association (ADA) publishes annual updates of standards of diabetes care (82), and in Sweden revised national guidelines of diabetes care were published in February 2010 (109). Guidelines include recommendations for the prevention and screening of complications, and focus on management recommendations concerning pharmacological treatment and lifestyle changes such as more physical activity and giving up smoking, as well as suitable ways to educate diabetes patients on their condition. Treatment target levels for glycaemic control, blood pressure and blood lipids in different guidelines are summarized in Table 1.

Table 1. Summary of main treatment target levels in different guidelines

	Sweden[1]	ESC/EASD[2]	ADA[3]
HbA1c (DCCT)	<7.0%	≤6.5%	<7.0%
Blood pressure	<130/80 mmHg	<130/80 mmHg	<130/80 mmHg
Total cholesterol		<4.5 mmol/L	
LDL cholesterol	<2.5 mmol/L	≤1.8 mmol/L (if previous CVD)	<2.5 mmol/L

[1] *National Board of Health and Welfare in Sweden National Guidelines on Diabetes Care in 2010.*
[2] *European Society of Cardiology and European Association for the Study of Diabetes: Practice Guidelines on Diabetes, Pre-diabetes and Cardiovascular Diseases in 2007.*
[3] *American Diabetes Association Standards of Diabetes Care in 2010.*

AIMS

• To describe the clinical characteristics and risk factors in patients with type 1 diabetes, and to evaluate the degree of fulfilment of treatment targets, and to analyse predictors of long-term successful glycaemic control

• To investigate the association between glycaemic control and CVD in type 1 diabetes, also with regard to effects of diabetes duration and albuminuria

• To investigate the association between BMI, overweight and obesity, and CVD and mortality in type 2 diabetes

• To investigate the association between glycaemic control and CVD and mortality in type 2 diabetes, also with regard to diabetes duration, previous CVD, and type of hypoglycaemic treatment

PATIENTS AND METHODS

THE SWEDISH NATIONAL DIABETES REGISTER

The Swedish National Diabetes Register (NDR) was initiated in 1996 in response to the St. Vincent Declaration of quality control in diabetes care (110). The overall objective of the St Vincent Declaration on diabetes care and research in Europe is to improve the quality of life and health of people with diabetes and ensure cost effectiveness in diabetes care (111). The main aim of the NDR is to improve diabetes care by monitoring care by encouraging the registration of data on all patients at least once a year. Health centres are able to use national results as benchmarking tools for quality control at their own unit, and adherence to treatment targets and national guidelines can be followed. Reporting to the NDR is not mandatory, but all hospital diabetes outpatient clinics and primary healthcare centres are encouraged to do so. All patients are informed about the register, and have agreed to be included.

Data on patients are reported annually by physicians, or nurses trained in diabetes care. Clinical characteristics, the results of laboratory tests, kind of treatment, complications and process measurements obtained during normal clinical visits are registered using a printed form or specifically developed computer software. Since 2001 it has been possible to report data via the Internet (www.ndr.nu), and since 2003 also by exporting data from electronic patient records. All information is subsequently stored in a central database. Data safety and confidentiality are maintained by the use of unique user names and passwords for each unit and encrypted Internet communication. The variables recorded in the Swedish NDR are listed in Table 2.

Table 2. Variables recorded in the Swedish NDR.

Registration date	Nephropathy (clinical diagnosis)
Personal identification number	Smoking status
Healthcare unit (code)	Previous CHD
Date of diabetes diagnosis	Previous stroke
Type of diabetes (voluntary)	Retinal screening
Type of hypoglycaemic treatment	Retinopathy
HbA1c	Foot examination
Weight, height, BMI	Blood lipid level (since 2002)
Blood pressure	Acetyl Salicylic Acid (ASA) medication (since 2002)
Antihypertensive medication	Waist circumference (since 2004)
Lipid-lowering medication	Physical activity (since 2004)
Albuminuria, s-creatinine	Hypoglycaemic events (since 2009)

Validation

A validation study was performed in 2005 in the region of Skåne, by the former head of the NDR, Anders Nilsson. Using the capture–recapture technique, data for 1017 patients (30% of all patients registered at hospital outpatients clinics in Skåne 2004) were compared with clinical records, showing that data entry was generally accurate (capture). The study showed that 94% (median, range 89-97%) of the variables were correctly entered. The study also showed that patients not registered differed only marginally from registered patients (recapture) (112). Local validation initiatives have also shown that registered data are generally accurate. Further validation studies in primary care are ongoing.

Number of patients

The number of registered patients has increased since the register was introduced in 1996, especially patients reported by primary healthcare centres (Figure 1). Hospital clinics have participated to a large extent from the beginning, and reported data on 26,361 patients in 1997, on 30,354 patients in 2003 and on 45,232 in 2009. Primary healthcare centres reported data on 14,793 patents in 1997, and since 2002 there has been a remarkable increase in both the number of patients included and the number of participating units; 49,289 patients in 2003 and over 210,000 patients in 2009. In total 262,333 patients were reported in 2009. Assuming the prevalence of diabetes to be 4% in Sweden, it was estimated that data on about 70% of all patients with diabetes
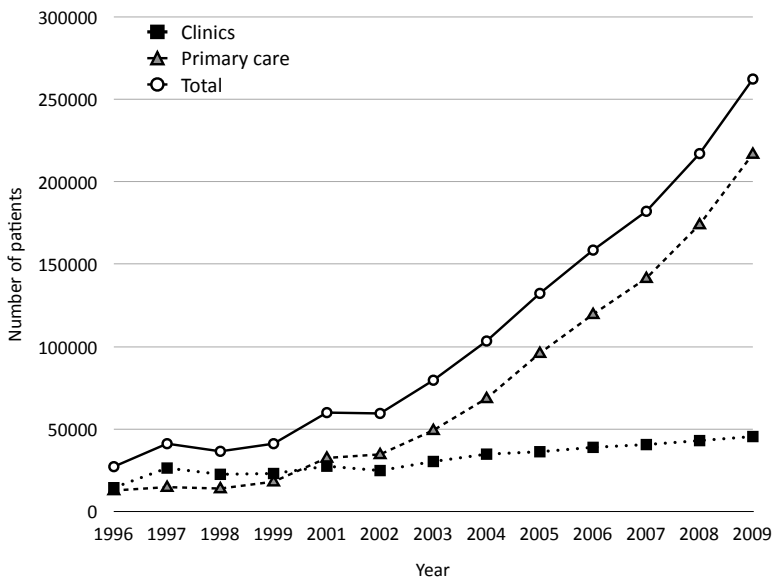

Figure 1. Number of patients registered in the Swedish NDR from 1996 to 2009.

were reported to the NDR in 2009. Coverage varied between counties from 40% (2 county health authorities) to 90% in 2009. A degree of coverage of about 70% was also found when comparing the number of patients in the NDR on oral hypoglycaemic agents (OHA) or insulin with the number of dispensed prescriptions for hypoglycaemic agents in the pharmaceutical register.

The Swedish NDR – A tool for quality control
The NDR offers the participating units possibilities for improving diabetes care. The NDR promotes education and the evaluation of the quality of care, in courses and in quality assurance projects, where the local units work with their own data and discuss improvement strategies. The units can obtain both technical and statistical support in analysing their own data. Online support providing print-outs for individual patients can be used in patient consultations.

METHODOLOGY
Brief overview of the study designs used in clinical research
Clinical research studies are usually divided into experimental and observational studies (113). In an experimental study, for example a randomized control trial, the investigator assigns the exposure whereas in observational studies the investigator observes an already existing exposure. The most common observational study designs are cohort studies, case-control studies and cross-sectional studies (113). In cohort studies the subjects are followed over time, information is gathered on characteristics and exposures at baseline, and the outcomes are studied over a given period of time. Cumulative incidence, incidence rates and relative risks can be estimated (114). In case-control studies, subjects with a particular outcome (the cases) and subjects without the outcome (the controls) are identified and then previous exposures between the two groups
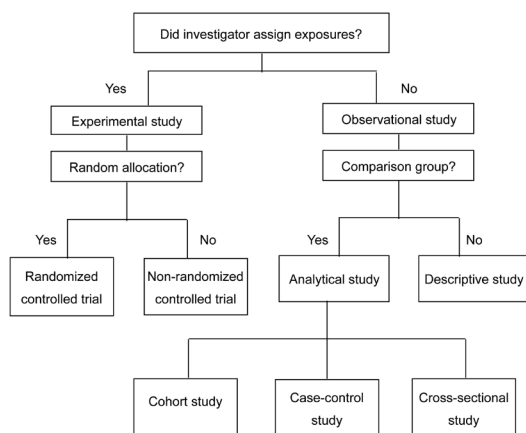
Figure 2: Algorithm for clinical research (adapted from reference 113).

are compared (115). The odds ratio between the cases and controls is interpreted as the relative risk. Cross-sectional studies assess all individuals at the same point in time, often to examine the prevalence of exposures, risk factors or disease (116).

Study design and participants in the present studies
The studies described in this thesis are all observational studies based on data from the NDR. Study I is a cross-sectional study, while Studies II, III and IV are longitudinal cohort studies. An overview of the study design, participants and main study characteristics is presented in Table 3. In Studies III and IV on type 2 diabetes, patients younger than 30 years were excluded due to the expected low risk of CVD, and patients older than 75 years (Study III) and 79 years (Study IV) were also excluded to avoid the effects of co-morbidity. In Study II, on type 1 diabetes, patients with long-standing diabetes were excluded as this group of patients is less likely to be representative of all patients (117). Patients with previous cardiovascular disease were included in Studies II and IV, as they are representative of the patients in a clinical setting. However, patients with and without a history of CVD were analysed separately in the study of type 2 diabetes (Study IV).

Table 3. Study design, patients and main inclusion criteria in the present studies.

Study	I	II	III	IV
Type of diabetes	Type 1 diabetes	Type 1 diabetes	Type 2 diabetes	Type 2 diabetes
Type of study	Cross-sectional	Cohort study	Cohort study	Cohort study
Number of patients	9424 and 13,612	7454	13,087	18,334
Baseline years	1997 and 2004	2002/2003	1997/1998	1997/1998
Patient age	≥ 18 years	20-65 years	30-74 years	30-79 years
Diabetes duration		1-35 years		
Follow-up time (end of study)		4.95 years (2007)	5.6 years (2003)	5.6 years (2003)
History of CVD at baseline		Yes (3%)	No	Yes (18%)
Key variable range		HbA1c 5.0-11.9%	BMI ≥18 kg/m^2	HbA1c 5.0-10.9%
Number of fatal/non-fatal CVD events (outcome)		154	1922	3823
Person-years		32,931	64,864	87,815

Study I

In Study I, on risk factor control in type 1 diabetes, clinical characteristics and risk factor control were analysed in two cross-sectional samples of 9424 patients in 1997 and 13,612 patients in 2004. Blood lipid levels were analysed in 2002 (n=6804) and 2004 (n=10,933). Logistic regression was used to analyse the predictors of long-term development of HbA1c and blood pressure in 4294 patients who were followed individually from 1997 to 2004.

Study II

In this study, examining glycaemic control and cardiovascular risk in type 1 diabetes, 7454 patients, aged 20-65 years, with a diabetes duration of 1-35 years, were followed from 2002 to 2007. The participants were also divided, at baseline, into subgroups of shorter and longer disease duration, and lower and higher HbA1c intervals, as outlined in Figure 3. Patients were followed-up for a mean period of 4.95 years, and the endpoint events were fatal or non-fatal CHD, fatal or non-fatal stroke, fatal or non-fatal CVD and total mortality.
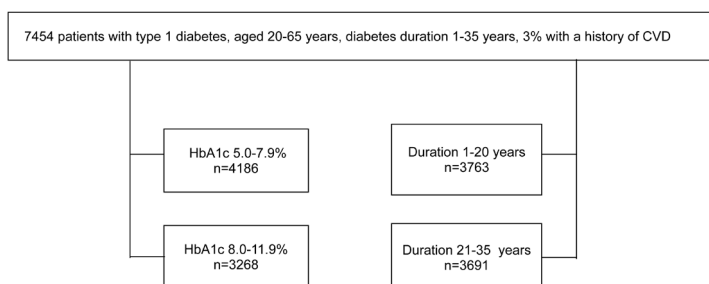
```
┌─────────────────────────────────────────────────────────────────────────┐
│ 7454 patients with type 1 diabetes, aged 20-65 years, diabetes duration   │
│ 1-35 years, 3% with a history of CVD                                      │
└─────────────────────────────────────────────────────────────────────────┘

        ┌──────────────────────┐          ┌──────────────────────┐
        │  HbA1c 5.0-7.9%      │          │  Duration 1-20 years  │
        │  n=4186              │          │  n=3763               │
        └──────────────────────┘          └──────────────────────┘

        ┌──────────────────────┐          ┌──────────────────────┐
        │  HbA1c 8.0-11.9%     │          │  Duration 21-35 years │
        │  n=3268              │          │  n=3691               │
        └──────────────────────┘          └──────────────────────┘
```

Figure 3. The design of Study II.

Study III

Associations between BMI, overweight and obesity, and cardiovascular risk in type 2 diabetes were assessed in Study III, where 13,087 patients, aged 30-74 years, with no previous history of CVD were followed from baseline until a cardiovascular event, death, or 31 December, 2003 (mean follow-up 5.6 years). BMI was analysed as a continuous variable per 5-unit increase, and in groups of normal weight, overweight and obesity, as shown in Figure 4. The following endpoints were analysed: fatal or non-fatal CHD, fatal or non-fatal stroke, fatal or non-fatal CVD, and total mortality. Change in BMI was analysed in a subgroup of 4,916 overweight or obese (BMI 25-40 kg/m^2) patients for whom data were available at baseline and at follow-up.

13,087 patients with type 2 diabetes, aged 30-74 years, BMI >18 kg/m^2

BMI <25kg/m^2
n=2676

Patients with BMI 25-40 kg/m^2 at baseline and known BMI at follow-up, n=4916

BMI 25-29.9 kg/m^2
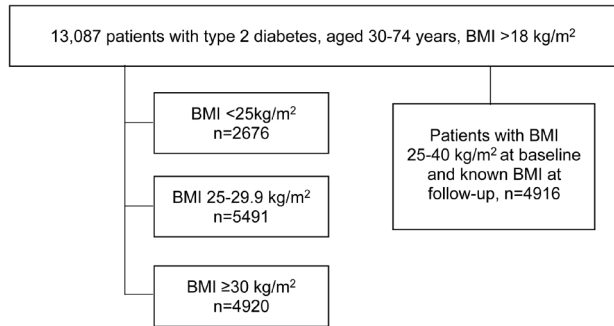n=5491

BMI ≥30 kg/m^2
n=4920

Figure 4. The design of Study III.

Study IV

In Study IV, on glycaemic control and CVD risk in type 2 diabetes, 18,334 patients, aged 30-79 years, of which 18% had a history of CVD, were followed for 6 years from 1997/98 to 2003. HbA1c was analysed as a continuous variable, and by comparison of groups with higher and lower HbA1c intervals. The effect of glycaemia was also ana-lysed in patients sub-grouped according to shorter (mean 3 years) or longer (mean 15 years) diabetes duration, by the presence or absence of previous CVD, or by treatment with oral hypoglycaemic agents (OHAs) or insulin (Figure 5). The mean follow-up period was 5.6 years, and the endpoint events were fatal or non-fatal CHD, stroke, CVD and total mortality.
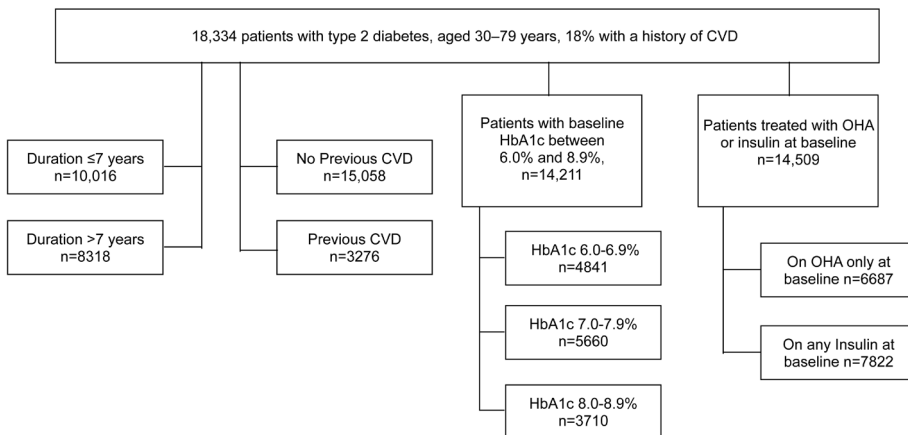

18,334 patients with type 2 diabetes, aged 30–79 years, 18% with a history of CVD

Duration ≤7 years
n=10,016

No Previous CVD
n=15,058

Patients with baseline HbA1c between 6.0% and 8.9%, n=14,211

Patients treated with OHA or insulin at baseline
n=14,509

Duration >7 years
n=8318

Previous CVD
n=3276

HbA1c 6.0-6.9%
n=4841

On OHA only at baseline n=6687

HbA1c 7.0-7.9%
n=5660

On any Insulin at baseline n=7822

HbA1c 8.0-8.9%
n=3710

Figure 5. The design of Study IV.

Definition of diabetes

Patients were diagnosed as having diabetes at their local outpatient clinic or primary healthcare centre according to current WHO criteria (1). In the present studies epidemiological definitions of type 1 and type 2 diabetes were used. The epidemiological definition of type 1 diabetes used in Studies I and II was: treatment with insulin only, and age at the onset of diabetes of 30 years or younger. In Studies III and IV the definition of type 2 diabetes was: a patient treated with dietary and lifestyle changes alone or OHAs alone, or age at onset of diabetes ≥40 years and treatment with insulin either alone or in combination with OHAs.

Register linkage procedure used to determine endpoint events

In Studies II, III and IV on cardiovascular disease risk, all endpoint events were retrieved by data linkage with the Swedish Cause of Death Register and the Hospital Discharge Register. These registers are supervised by the National Board of Health and Welfare in Sweden, and reporting has been mandatory since 1987. Cardiovascular diagnoses in the Hospital Discharge Register have been validated, showing a high degree of validity, approximately 95% for MI and stroke, and 82% for CHF, when compared with hospital records (118-121). Register linkage is possible in Sweden since all Swedish permanent residents have a unique 12-digit personal identification number. After ethical approval, and separate approval from the National Board of Health and Welfare, the file containing the NDR data was sent to the epidemiological centre at the National Board of Health and Welfare, where the merge was done and the new file was returned to the NDR with a new, unique identification number for each patient. The first linkage was performed in 2005 with complete information on hospital discharge diagnosis and mortality until 31 December 2003 (Studies III and IV), and the second in 2009, including information up until 31 December 2007 (Study II).

Definition of CVD events

The International Classification of Diseases, version 9 (ICD-9), was used from 1987 to 1996, and version 10 (ICD-10) after 1997. The cardiovascular endpoint events were defined according to ICD-9 or ICD-10 codes, as well as the history of CVD, history of congestive heart failure, dating back to 1987 (http://www.who.int/ classifications/icd/ en/). Fatal CHD was defined as ICD-10 codes I20–I25. Non-fatal CHD was defined as non-fatal myocardial infarction (MI) (ICD-10 code I21), unstable angina (ICD-10 code I20.0), percutaneous coronary intervention and/or coronary artery bypass grafting. Stroke was defined as a fatal or non-fatal cerebral infarction, intracerebral haemorrhage or unspecified stroke (ICD-10 codes I61, I63, I64 and I67.9). CVD was defined as the composite of CHD or stroke, whichever occurred first, and the same definition was used for a history of CVD at baseline. A history of congestive heart failure (CHF) at baseline was defined as ICD-10 code I50. Peripheral vascular disease was not included.

Clinical characteristics at baseline and laboratory testing

The clinical characteristics analysed in the cross sectional study (Study I) and at baseline in Studies II, III and IV were age, sex, diabetes duration, HbA1c level, type of hypoglycaemic treatment, BMI, smoking status, blood pressure, use of antihypertensive medication and lipid-lowering medication, and albuminuria. Blood lipid levels and use of acetyl salicylic acid (ASA) have been registered since 2002, and were considered in Studies I and II. Patients were screened using local methods, although guidelines were available to ensure the use of similar methodology. Analyses of HbA1c, blood lipids and albuminuria were carried out at local laboratories. The BMI was calculated as weight (kg) divided by height (m) squared. The Swedish standard for blood pressure recording was used, and applied as the mean of two readings (Korotkoff phases 1-5), with the patient sitting or lying down, using a cuff of appropriate size. Hypertension (Study I) was defined as untreated blood pressure ≥140/90 mmHg or antihypertensive treatment using the current WHO and ADA definition (1, 82). A smoker was defined as a patient who smoked one or more cigarettes per day, or a pipe daily, or who had stopped smoking within the past 3 months. LDL cholesterol values were calculated using Friedewald's formula: LDL cholesterol = total cholesterol – HDL cholesterol – (0.45 x triglycerides), if triglycerides <4.0 mmol/l (122). Albuminuria was defined as urine albumin excretion >20 μg/min, including microalbuminuria (20-200 μg/min) or macroalbuminuria (>200 μg/min) in two out of three consecutive tests.

HbA1c analyses have been quality assured in Sweden since 1996. Both hospital outpatient clinics and primary healthcare centres use methods regularly calibrated to the Mono-S standard, a high-performance liquid chromatography method. All HbA1c values were converted into the DCCT standard levels: HbA1c (DCCT) = 0.923 x HbA1c (Mono-S) + 1.345; R2=0.998 (91). In Studies II and IV, HbA1c was measured at baseline and also over time as an updated mean of annual HbA1c measurements, calculated for each individual from baseline to each year of follow-up, with the last observation carried forward in the case of missing data. In cases of a cardiovascular event or death during follow-up, the period used to estimate the updated mean HbA1c was from baseline to the year before the event occurred, otherwise from baseline to the date of censor.

STATISTICAL METHODS
Basic concepts in survival analysis
In survival analysis, the outcome variable of interest is the time until an event occurs (123). This is called the survival time, as the event is often death, but the event of interest can also be a non-fatal event. A key feature of survival analysis is taking into account the censoring effect. Censoring arises when a patient has not suffered an event by the end of the follow up period, is lost to follow-up, or experiences another event that makes follow-up impossible. The survival probability (survival function) is the probability of surviving from the start of the study to a specified time in the future. The hazard probability can be described as the instantaneous risk of an event, given that the individual has survived until that point. The Kaplan-Meier and Cox proportional hazards models are two methods frequently used in survival analysis (123).

The Kaplan-Meier method
The Kaplan-Meier method is a non-parametric method, and Kaplan-Meier survival curves describe the relationship between survival probability and follow-up time. This information is usually presented as curves, but can also be presented as the survival probability at a certain time. The follow-up time is usually divided into equal intervals, and the survival probability is the proportion of individuals alive at a certain time, of those known to be alive in the previous time interval (patients at risk) (123). It is a univariate analysis as it describes survival as a result of one factor, and the analysis cannot be adjusted for other factors (covariates) (124).

Cox proportional hazards model
The Cox proportional hazards model, also referred to as the Cox regression model, is a semi-parametric model and one of the most commonly used models in survival analysis. It is a survival analysis regression model describing the relations between event incidence, as expressed by the hazard function, and a set of covariates (124). The model requires proportional hazards, which means that the hazard ratio (HR), i.e. the relative hazard between two groups, is constant over time. The results are presented as HRs, and a value above 1.0 indicates a higher risk for the outcome in the first group versus the second, whereas a HR less than 1.0 indicates a lower risk in the first group compared with the second (124).

The smoothing spline is a method of smoothing (fitting a smooth curve to a set of noisy observations) using a spline function. The cubic regression spline produces visibly smooth curves, increasing the transparency of data for statistical presentation, and facilitating clinical interpretation (125).

Statistical methods used in the studies

All statistical analyses were performed using SAS version 9.1.3, (SAS Institute, Cary, NC, USA). A p- value <0.05 at two-tailed test was considered statistically significant.

Data are given as mean values ± one standard deviation (SD) for continuous variables, and as percentages for categorical variables. The significance of differences was estimated with Student's t-test for mean values, X^2 test for frequencies. Significance levels for trends of differences between groups were analysed using ANOVA (analysis of variance) for mean values and the X^2 test for frequencies. In Study I logistic regression was used to explore possible predictors of long-term control of HbA1c and blood pressure as nominal, dependent variables, and with clinical characteristics at baseline as the continuous or nominal predictors.

In Studies II and IV Cox proportional hazards models were used to estimate adjusted hazard ratios and 95% confidence intervals, for the outcomes CHD, stroke, CVD and total mortality per 1%-unit increase in baseline HbA1c or updated mean HbA1c, and also to compare higher and lower intervals of baseline HbA1c. The updated mean HbA1c value was treated as a strictly time-dependent variable in the Cox regression model to evaluate glycaemic exposure during follow-up. In Study II HRs were adjusted for age, sex, diabetes duration, systolic blood pressure, total cholesterol, LDL cholesterol, triglycerides, BMI, smoking, albuminuria and history of CVD, unless stated otherwise. In Study IV HR were adjusted for sex, age, diabetes duration, BMI, smoking status, systolic blood pressure, antihypertensive and lipid-lowering drug use, albuminuria >20 µg/min, type of hypoglycaemic treatment, history of CVD and history of congestive heart failure, unless stated otherwise. Continuous covariates were analysed per 1-unit increase in the models.

In Study III adjusted hazard ratios for BMI (per 5-unit increase), overweight and obesity at baseline and first-incident cardiovascular events were estimated using Cox proportional hazards models, also used to estimate adjusted HRs for changes in BMI during the study period and the outcomes in a subgroup of overweight or obese patients. Model 1 adjusted for age, sex, type of hypoglycaemic treatment, diabetes duration, smoking and significant interactions. Model 2 also adjusted for HbA1c, systolic blood pressure, antihypertensive and lipid-lowering medication and albuminuria.

In Studies II, III and IV the proportional hazards assumption was tested for all covariates in the models with the Kolmogorov-type Supremum test using resampling, and with Test of all time-dependent covariates simultaneously (126), and confirmed that this assumption was not rejected for any of the included covariates (p >0.05). Interactions were tested using Maximum likelihood estimations. In Study II there was no significant interaction between HbA1c and the covariates included, whereas in Study IV, on type 2 diabetes, there was a significant interaction between HbA1c and diabetes duration. Analysis stratified by shorter and longer duration was included. In Study III

the interaction between BMI and the change in BMI, and all covariates was analysed with maximum likelihood estimation, and significant interaction variables were added in all Cox regression analyses.

In the two most recent studies (II and IV), a Cox regression model was also used to estimate 5-year event rates (1 – survival rate) in Study II, and 6-year event rates in Study IV, for cardiovascular diseases, where the model output was the adjusted 5-year event rate (or 6-year event rate) in each participant, adjusted for covariates, as given in the tables and figures (127). These event rates were also analysed as splines in relation to HbA1c across the range (125). Stratification was performed to achieve adjusted mean event rates (± SD) by groups or deciles of lower and higher HbA1c. The significance level for the difference in mean event rates between the two groups with lower and higher baseline HbA1c intervals was analysed with Student's t-test, after logarithmic transformation of the event rates to achieve a normal distribution. In Study IV, Kaplan-Meier observed 6-year failure rates were also estimated at survival analysis in each group of different HbA1c levels, for calibration of the mean event rates.

ETHICAL CONSIDERATIONS
The Regional Ethics Review Board at the University of Gothenburg approved the studies.

MAIN RESULTS

STUDIES ON TYPE 1 DIABETES

The results of the cross sectional study of all patients in 1997 and 2004 (Study I), are summarized in Table 4 (following page), together with, the baseline characteristics in the cohort study on glycaemia control and CVD risk in type 1 diabetic patients, aged 20-65 years with a duration of diabetes of 1-35 years, (Study II).

Cross-sectional results (Study I)

The cross sectional surveys showed an almost unchanged mean age of 39-42 years and mean diabetes duration of 23-26 years between 1997 and 2004, unchanged mean age of debut of 15 years and unchanged proportion of women (46%). Slight, but significant improvements in HbA1c levels, blood pressure and lipid levels were seen together with a small increase in BMI. Significantly more patients were also being treated with lipid-lowering and antihypertensive medication in 2004 than in 1997; the most marked change being that in lipid-lowering medication, with an increase from 4% in 1997 (20% in 2002) to 24% in 2004. The rate of smoking decreased from 15% to 13%, and was highest in younger women and middle-aged patients. Repeated control of eye and foot status were performed in almost all patients in 2004.

The percentages of patients reaching the treatment target levels for glycaemia, blood pressure, blood lipid levels and BMI are presented in Table 5. The proportions of patients reaching the treatment target of HbA1c <7% were 17% in 1997 and 21% in 2004. Over half of the patients (56%) reached an HbA1c level <8% in 2004. More patients reached both blood pressure and lipid target levels in 2004. Those achieving blood pressure ≤130/80 mmHg constituted 61% in 2004, and about half of the patients achieved LDL cholesterol <2.5 mmol/L. Although an increase was seen in the number of obese patients (from 8% to 10%), over 50% were still of normal weight in 2004.

Longitudinal study (Study I)

The longitudinal study comprised a subgroup of 4296 patients with type 1 diabetes that could be followed individually from 1997 to 2004. Logistic regression analysis showed that long-term successful glycaemic control (HbA1c <7.3% in 1997 and in 2004) was independently predicted by low BMI, not smoking and the absence of microalbuminuria at baseline. Successful long-term BP control (BP <130/80 mmHg in 1997 and 2004) was predicted by low BMI and the absence of microalbuminuria at baseline, and by weight loss during the period, independently of age, sex, duration of diabetes and the use of antihypertensive drugs.

Table 4. Comparison of clinical characteristics in the cross sectional samples of patients with type 1 diabetes in 1997 and 2004, and the baseline characteristics 2002/2003 in the study on CVD risk in type 1 diabetes.

	Study I All patients age ≥18 years			Study II Age 20-65 yrs Duration 1-35 yrs
	1997	2004	p-value	2002/2003
Number	9424	13,612		7454
Age, y	38.6±13	41.6±14	<0.001	36.9±10.0
Male sex, %	54.4	54.5	n.s.	55.8
Duration, y	23.1±13	26.1±14	<0.01	19.9±9.1
HbA1c, %	8.16±1.3	7.96±1.2	<0.001	8.0±1.2
Systolic BP, mmHg	130.0±18	128.7±17	<0.001	125.3±14.9
Diastolic BP, mmHg	75.0±9	73.6±9	<0.001	-
Antihypertensive drugs, %	23.0	33.9	<0.001	24.4
Hypertension, %	42.4	45.5	<0.001	-
Lipid-lowering drugs, %	4.0	24.4	<0.001	16.6
BMI, kg/m^2	24.9±3.5	25.3±3.9	<0.001	25.3±3.7
Smokers, %	15.1	13.3	<0.001	13.5
Age <30 years, women, %	15.4	16.0	n.s.	-
Age <30 years, men, %	9.0	9.3	n.s.	-
Age 30-59 years, %	17.0	14.3	<0.001	-
Age >60 years, %	8.8	9.0	n.s.	-
	2002 n=6804	2004 n=10,933		2002/2003 n=7454
Total Cholesterol, mmol/L	4.93±0.91	4.78±0.9	<0.001	4.82±0.9
LDL Cholesterol, mmol/L	2.82±0.80	2.67±0.8	<0.001	2.75±0.8
HDL Cholesterol, mmol/L	1.61±0.47	1.62±0.5	n.s.	-
Triglycerides, mmol/L	1.12±0.58	1.08±0.6	<0.01	1.09±0.6
ASA, %	11.9	16.8	<0.001	6.8

The values given are means ± SD or frequencies (%). Significance levels in Study I were tested with general linear model and were adjusted for age and sex. n.s: not significant.

Glycaemic control and CVD risk in type 1 diabetes (Study II)

Baseline characteristics are given in Table 4 for all 7474 patients with type 1 diabetes, aged 20-65 years, with 1-35 years of diabetes duration; 3% of the patients had a history of CVD. The patients were also divided into two groups with lower or higher baseline HbA1c intervals, where the group with higher HbA1c had a somewhat more adverse

risk factor profile. Cox proportional hazards models were used to assess the risk of cardiovascular diseases and total mortality. The mean follow-up time was 4.95 years, and 154 CVD events occurred during this time. Crude event rates per 1000 person-years were 4.0 for CHD, 1.1 for stroke, 4.7 for CVD and 2.8 for total mortality. HbA1c was analysed as a continuous variable, and the two groups with higher and lower HbA1c at baseline were compared.

Table 5. Comparison of risk factor control in samples of patients with type 1 diabetes registered in the NDR in 1997 and 2004.

All patients	1997	2004	p-value
Number	9424	13 612	
HbA1c <7 %	17.4	21.2	<0.001
HbA1c <8 %	49.1	56.2	<0.001
HbA1c <9 %	76.7	81.9	<0.001
Blood pressure <130/80, %	35.2	39.3	<0.001
Blood pressure ≤130/80, %	58.1	61.3	<0.001
Blood pressure ≤140/85, %	77.1	80.6	<0.001
BMI <25, %	56.2	52.3	<0.001
BMI ≥30, %	8.1	10.5	<0.001
Patients treated with lipid-lowering medication:	2002 n=1474	2004 n=2738	
Total Cholesterol <4.5 mmol/L, %	27.7	37.7	<0.001
LDL Cholesterol <2.5 mmol/L, %	38.3	48.1	<0.001
Triglycerides <1.7 mmol/L, %	75.9	80.9	<0.01

The values given are frequencies (%). Significance levels of trend for frequencies were adjusted for age and sex using the general linear model.

HbA1c as a continuous variable
Table 6 (following page) gives hazard ratios per 1%-unit increase in baseline HbA1c or updated mean HbA1c in all patients and in those sub-grouped according to median duration. HRs for CHD and CVD per 1%-unit increase in HbA1c were 1.31 and 1.26 (p<0.001), respectively, when adjusted for age, sex, diabetes duration, systolic blood pressure, total and LDL cholesterol, triglycerides, BMI, smoking, and a history of CVD (Model 1). Risks were slightly attenuated, but still significant, when also adjusted for albuminuria (Model 2). Similar HRs were seen when using updated mean HbA1c values. Significant HRs were also seen in patients with both shorter (mean 12 years) and longer durations (mean 28 years) of diabetes. The HRs for stroke and total mortality were not significant. Adjusted 5-year event rates of CHD and CVD by base

Table 6. Hazard ratios for cardiovascular diseases and total mortality, and baseline or updated mean HbA1c per 1%-unit increase, in 7454 patients with type 1 diabetes followed for 5 years.

Outcome	Patients/ Events/ Mean event rate, % [a]	Baseline HbA1c as predictor		Updated mean HbA1c as predictor	
		HR (95% CI) Model 1	HR (95% CI) Model 2	HR (95% CI) Model 1	HR (95% CI) Model 2
Fatal/non-fatal CHD					
All patients	7454 / 131 / 2.0	1.31 (1.12-1.52) [1]	1.28 (1.09-1.49) [2]	1.34 (1.14-1.58) [1]	1.30 (1.10-1.53) [2]
Duration 1–20 years	3763 / 25 / 0.8	1.49 (1.08-2.05) [3]	1.46 (1.06-2.01) [3]	1.45 (1.03-2.03) [3]	1.41 (1.01-1.97) [3]
Duration 21–35 years	3691 / 106 / 3.2	1.30 (1.10-1.54) [2]	1.27 (1.07-1.50) [2]	1.38 (1.15-1.67) [1]	1.34 (1.11-1.62) [2]
Fatal/non-fatal stroke					
All patients	7454 / 37 / 0.6	1.12 (0.83-1.51)	1.08 (0.80-1.47)	1.24 (0.89-1.72)	1.19 (0.86-1.66)
Fatal/non-fatal CVD					
All patients	7454 / 154 / 2.4	1.26 (1.09-1.45) [1]	1.22 (1.06-1.40) [2]	1.32 (1.14-1.54) [1]	1.27 (1.09-1.80) [2]
Duration 1–20 years	3763 / 26 / 0.8	1.49 (1.09-2.04) [3]	1.46 (1.07-2.00) [3]	1.48 (1.06-2.07) [3]	1.44 (1.04-2.01) [3]
Duration 21–35 years	3691 / 128 / 4.0	1.23 (1.06-1.44) [2]	1.19 (1.02-1.39) [3]	1.34 (1.13-1.59) [1]	1.29 (1.08-1.53) [2]
Total mortality					
All patients	7454 / 94 / 1.4	0.97 (0.80-1.17)	0.92 (0.76-1.11)	1.04 (0.85-1.28)	0.98 (0.80-1.20)

CI: confidence interval. HR: Hazard ratio. Model 1: Adjusted for age, sex, diabetes duration, systolic blood pressure, total cholesterol, LDL cholesterol, triglycerides, BMI, smoking, and a history of CVD. Model 2: Adjusted as in Model 1 and also for albuminuria (>20 µg/min). [a] Mean event rates in a Cox model adjusted as in Model 2. Significance level for hazard ratios: [1] p <0.001, [2] p <0.01, [3] p <0.05.

line HbA1c or updated mean HbA1c ranging from 5% to 12% are presented for all patients in Figure 6 A and B, and according to duration in Figure 6 E-H, showing increasing event rates with higher HbA1c. No elevated risk was seen at the lowest HbA1c levels, as also verified by mean CHD and CVD event rates by deciles of updated mean HbA1c, Figure 6 C-D.

Intervals of HbA1c
The group of 3268 patients with higher HbA1c values at baseline (8.0-11.9%, mean 9.0%) had a HR of 1.71 for CHD (95% confidence interval (CI) 1.18-2.48); $p<0.01$, and 1.59 for CVD (1.13-2.24); $p<0.01$, (also adjusted for albuminuria) compared with the group of 4816 patients with lower baseline HbA1c values (5.0-7.9%, mean 7.2%), followed for five years. This corresponds to a risk reduction of 41% for CHD and 37% for CVD, in the group with lower baseline HbA1c.
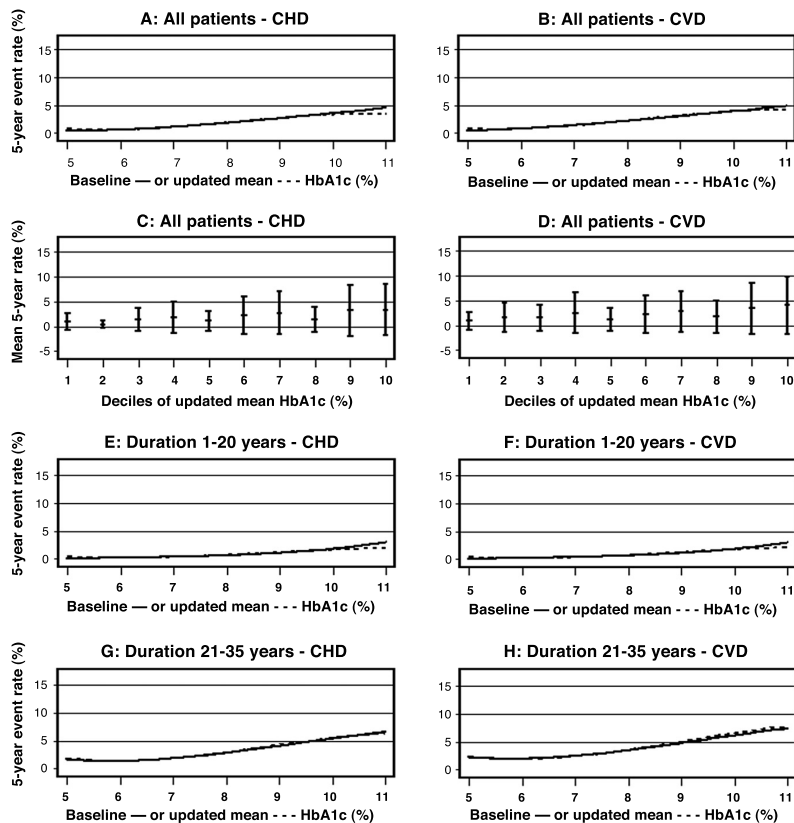
Figure 6. Five-year rates (%) of fatal/non-fatal CHD and CVD in a fully adjusted Cox model. A-B: Splines for event rates in all 7454 patients, as a cubic function of baseline HbA1c (solid line) and updated mean HbA1c (dashed line). C-D: Adjusted mean rates (±SD) by deciles of updated mean HbA1c; the solid line showing the linear association by deciles. E-H: Splines for event rates in subgroups by median duration 20 years.

STUDIES ON TYPE 2 DIABETES

An overview of the baseline characteristics in Study III on BMI, overweight and obesity and CVD risk, and in Study IV on glycaemia control and CVD risk is presented in Table 7.

Table 7. Clinical characteristics at baseline in 1997/1998 in Studies III and IV. The data are given as mean ± standard deviation (SD), and frequency (%) for categorical variables.

Characteristic	Study III (BMI) Age 30-74 years, no previous CVD	Study IV (HbA1c) Age 30-79 years
Number	13,087	18,334
BMI, kg/m^2	29.1±5	28.8±5
Age, years	60±9	64±10
Diabetes duration, years	9±7	8±7
HbA1c, %	7.6±1.3	7.6±1.2
Systolic blood pressure, mmHg	146±18	148±19
Male sex, %	55.7	56.7
Smokers, %	16.4	14.2
Antihypertensive drugs, %	47.0	53.8
Lipid-lowering drugs, %	12.6	15.6
Albuminuria, % (>20 µg/min)	20.9	23.2
Diet treatment, %	21.7	20.9
OHA, %	36.6	36.5
OHA and insulin, %	12.1	12.9
Insulin, %	29.5	29.7
History of CVD	-	17.9
History of Congestive heart failure (CHF)	-	6.4

BMI, overweight and obesity and CVD risk (Study III)

Of 13,087 patients with type 2 diabetes with BMI ≥ 18 kg/m2 and no previous CVD, 20% were of normal weight (BMI< 25 kg/m2), 42% overweight (BMI 25-29.9 kg/m^2), and 38% were obese (BMI ≥30 kg/m2). Overweight and obese patients had shorter diabetes duration, higher HbA1c, and higher systolic blood pressure; microalbuminuria was more frequent and smokers less frequent, compared with patients of normal weight. During the period of the study, there were 1922 CVD events; based on 64,864 person-years, this gives a crude incidence rate of 29.6 events per 1000-person years.

BMI as continuous variable

Cox regression analyses were performed on the data for all 13,087 patients, followed up for a mean period of 5.6 years, to determine hazard ratios (and 95% confidence intervals) for BMI at baseline as a continuous variable and first-incident fatal or non-fatal CHD, stroke, CVD, and total mortality. The results are presented in Table 8. For a 5-unit increase in BMI the adjusted hazard ratios were 1.15 for CHD, 1.11 for stroke, 1.13 for CVD and 1.27 for total mortality, which were significant after adjustment for age, sex, diabetes duration, type of hypoglycaemic treatment, smoking and significant interactions (Model 1). The risks were attenuated, but remained significant, except for stroke, after also adjusting for HbA1c, microalbuminuria, systolic blood pressure, and lipid-lowering and hypertensive treatment (Model 2).

Table 8. Hazard ratios for BMI per 5-unit increase as predictor, and first incident fatal/ non-fatal CHD, stroke and CVD, and total mortality, at Cox regression analysis of data from 13,087 type 2 diabetic patients, followed up for 6 years.

Outcome	Events	Model 1[a] HR (95% CI)	p-value	Model 2[b] HR (95% CI)	p-value
Fatal/non-fatal CHD	1326	1.15 (1.08-1.21)	<0.001	1.09 (1.03-1.16)	0.0026
Fatal/non-fatal stroke	756	1.11 (1.03-1.19)	0.0090	1.04 (0.96-1.12)	n.s.
Fatal/non-fatal CVD	1922	1.13 (1.08-1.18)	<0.001	1.07 (1.02-1.12)	0.0073
Total mortality	664	1.27 (1.17-1.37)	<0.001	1.20 (1.10-1.30)	<0.001

HR = Adjusted hazard ratio. CI = Confidence interval. [a] Model 1: Adjusted for age, sex, type of hypoglycaemic treatment, diabetes duration, smoking and significant interactions. [b] Model 2: As in Model 1, and also adjusted for HbA1c, systolic blood pressure, antihypertensive drugs, lipid-lowering drugs and albuminuria (>20 µg/min).

Overweight and obesity compared with normal weight

Compared with normal weight, obesity was associated with an almost 50% increase in risk of CHD and CVD, and a 70% increase in risk of total mortality after adjusting for age, sex, type of hypoglycaemic treatment, diabetes duration and smoking. Overweight also increased the risk of CHD and CVD by about 20-30%, compared with normal weight, whereas the relative risk for total mortality was not significantly increased (Table 9; following page).

Change in BMI during the study

The change in BMI during 6 years, from baseline to follow-up in 2003, was analysed in a subgroup of 4,916 patients with baseline BMI 25-40 kg/m². The patients who gained most weight during the study (median increase in BMI 3.8 kg/m²) had increased HRs of 1.8-2.3 for CHD and 1.5-1.7 for CVD, compared with those who gained a little weight (median increase in BMI 1.0 kg/m²), those who lost a little (median loss 1.0 kg/m²), and those who lost most weight (median loss 4.0 kg/m²).

Table 9. Hazard ratios for overweight (BMI 25-29.9 kg/m²) and obesity (BMI ≥30 kg/m²) at baseline, compared with normal weight (BMI <25 kg/m²) and first-incident fatal/non-fatal CHD and CVD, and total mortality.

Outcome	BMI kg/m²	Patients n	Events n	Model 1[a] HR (95% CI)	p-value
Fatal/non-fatal CHD	25-29.9	5491	585	1.27 (1.09-1.48)	0.0028
	<25	2676	224	1.0	
Fatal/non-fatal CVD	25-29.9	5491	839	1.24 (1.09-1.41)	<0.001
	<25	2676	334	1.0	
Total mortality	25-29.9	5491	269	1.16 (0.94-1.45)	n.s.
	<25	2676	118	1.0	
Fatal/non-fatal CHD	≥30	4920	517	1.49 (1.27-1.76)	<0.001
	<25	2676	224	1.0	
Fatal/non-fatal CVD	≥30	4920	749	1.44 (1.26-1.64)	<0.001
	<25	2676	334	1.0	
Total mortality	≥30	4920	277	1.71 (1.36-2.14)	<0.001
	<25	2676	118	1.0	

[a] *Model 1: Adjusted for age, sex, type of hypoglycaemic treatment, diabetes duration, smoking and significant interactions.*

Glycaemia control and CVD risk in type 2 diabetes (Study IV)

The baseline clinical characteristics of all 18,334 patients are given in Table 7. Patients with previous CVD were included in this study and represent about one fifth of the patients at baseline. There were 3823 CVD events in all patients, giving a crude incidence rate of 43.5 per 1000 person-years, based on 87,815 person-years.

HbA1c as a continuous variable
The hazard ratios per 1%-unit increase in baseline HbA1c were 1.11 for fatal/non-fatal CHD, 1.08 for fatal/non-fatal stroke, 1.10 for fatal/non-fatal CVD, and 1.09 for total mortality, all p<0.001, after adjustment for cardiovascular risk factors. The results are given in Table 10. Slightly higher increases in significant risk, of about 10-13% per 1%-unit increase in HbA1c, were also seen when using updated mean HbA1c.

Table 10. Six-year mean rates (%) of CHD, stroke, CVD and total mortality, and hazard ratios for these outcomes per 1%-unit increase in baseline HbA1c in Cox regression analyses of the data for all patients (n=18,334) with type 2 diabetes followed for 6 years, and by diabetes duration, ≤7 years (n=10,016) or >7 years (n=8,318).

Outcome	Patient group	Events n	Event rate[a] Mean (SD)	Baseline HbA1c HR (95% CI)[b]	p-value
Fatal/non-fatal CHD	All patients	2623	16.6 (10.1)	1.11 (1.07–1.15)	<0.001
	Duration ≤7 years	1111	12.9 (8.2)	1.09 (1.03–1.15)	0.003
	Duration >7 years	1512	21.3 (10.4)	1.11 (1.06–1.16)	<0.001
Fatal/non-fatal stroke	All patients	1574	10.4 (7.1)	1.08 (1.03–1.13)	0.002
	Duration ≤7 years	657	8.1 (6.3)	1.06 (0.98–1.14)	0.1
	Duration >7 years	917	13.1 (7.1)	1.07 (1.01–1.14)	0.03
Fatal/non-fatal CVD	All patients	3823	23.9 (13.8)	1.10 (1.07–1.13)	<0.001
	Duration ≤7 years	1625	18.9 (11.9)	1.08 (1.03–1.13)	0.001
	Duration >7 years	2198	30.0 (13.7)	1.10 (1.06–1.14)	<0.001
Total mortality	All patients	1902	12.1 (11.8)	1.09 (1.05–1.14)	<0.001
	Duration ≤ 7 years	715	8.3 (9.0)	1.13 (1.05–1.21)	<0.001
	Duration >7 years	1187	16.7 (12.4)	1.07 (1.01–1.13)	0.01

[a] *Adjusted in a Cox model for sex, age, diabetes duration, BMI, smoking status, systolic BP, antihypertensive and lipid-lowering drug treatment, albuminuria (>20 µg/min) and type of hypoglycaemic treatment.* [b] *Hazard ratios per 1%-unit increase in baseline HbA1c, adjusted as in* [a].

Corresponding adjusted 6-year rates for these outcomes increased progressively with higher baseline and updated mean HbA1c values across the HbA1c range 5-11%, (Figure 7 A-D; following page). This was also the case in the analysis of mean 6-year rates of these outcomes by deciles of updated mean HbA1c (Figure 7 I-J).

The patients were divided into two subgroups according to the median duration of diabetes: ≤7 years (mean 3 years) and >7 years (mean 15 years) (Table 10). HRs for CHD and CVD and total mortality per 1%-unit increase in HbA1c were significant in both subgroups: HR 1.11-1.13 in the longer duration group and 1.07-1.09 in the shorter duration group. Figure 7 E-F shows that 6-year rates of fatal/non-fatal CVD, fatal CVD and total mortality increased with higher baseline and updated mean HbA1c values in both subgroups, although at a higher rate in the group with longer disease duration.

Adjusted 6-year rates of all outcomes were higher in the subgroup with previous CVD (n=3,276) than in that with no previous history of CVD (n=15,058). HRs for CHD, stroke, CVD and total mortality per 1%-unit increase in HbA1c were significant in both subgroups. Figure 7 G-H shows increasing 6-year outcome rates with higher HbA1c; at a higher rate among those with previous CVD. There was no risk increase at low HbA1c levels in either subgroup.

Groups with different levels of HbA1c at baseline
Three subgroups with baseline HbA1c levels of 6.0-6.9% (mean 6.5%), 7.0-7.9% (mean 7.5%) and 8.0-8.9% (mean 8.5%) were compared. According to the adjusted HRs, there was a risk reduction of 20% for CHD (p<0.001) and 16% for CVD (p<0.001) in the group with the lowest HbA1c (6.0-6.9%), compared with the group with 7.0-7.9% HbA1c. Even higher risk reductions (about 25%) for CHD and CVD, as well as a 22% reduction in the risk of fatal CVD (p<0.01), and 16% in total mortality (p<0.05), were found when the 6.0–6.9% HbA1c group was compared with the 8.0–8.9% HbA1c group.

Baseline treatment with OHAs or insulin
Insulin-treated patients had significantly increased risk of all outcomes except non-CVD mortality per 1%-unit higher HbA1c, whereas OHA-treated patients had significantly increased risk of fatal/non-fatal CHD and CVD, but not of fatal CVD, total mortality or non-CVD mortality, when also adjusted for history of CVD and CHF. Insulin-treated patients had progressively increasing rates of CVD and total mortality with increasing HbA1c level, whereas this trend was less pronounced among OHA-treated patients. There was no J-shaped risk curve with increased risk at low HbA1c levels in either subgroup. No significant increase in risks of fatal/non-fatal CHD or CVD were seen in the insulin-treated group compared with the OHA-treated group when adjusting for all covariates including a history of CVD and congestive heart failure (CHD) (Figure 8). The HR for total mortality was significant, and the increased
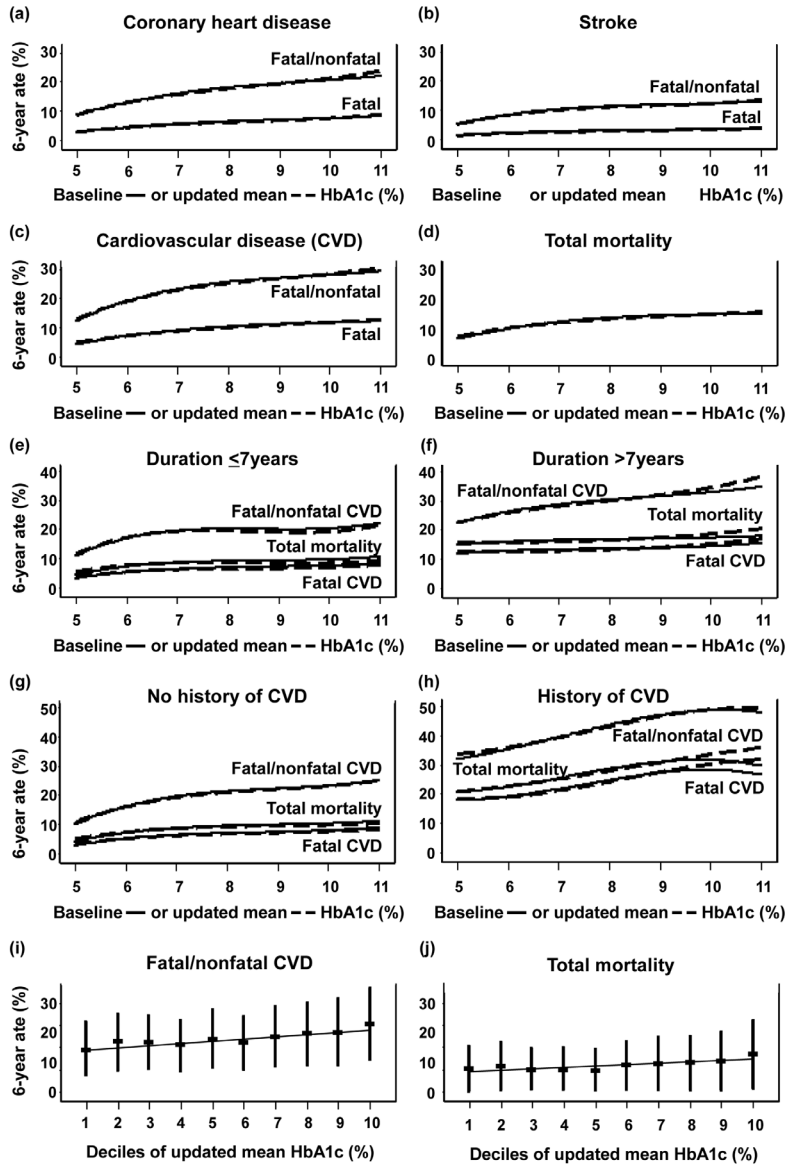
Figure 7. Six-year rates of CHD, stroke, CVD and total mortality as a cubic function of baseline HbA1c (solid line) and updated mean HbA1c (dashed line) in a Cox model adjusted as described in Table 10.

Results are shown for all 18,334 patients (A-D), for two subgroups with median diabetes duration: ≤7 years (n=10,016; E) and >7 years (n=8,318; F) and in two subgroups without (n=15,058; G) and with previous CVD (n= 3,276; H). I-J: Mean 6-year rates of CVD and total mortality by deciles of updated mean HbA1c in all 18,334 patients; the solid line shows the linear association between deciles.

risk of fatal CVD was weakly significant, whereas non-CVD mortality was highly significant.
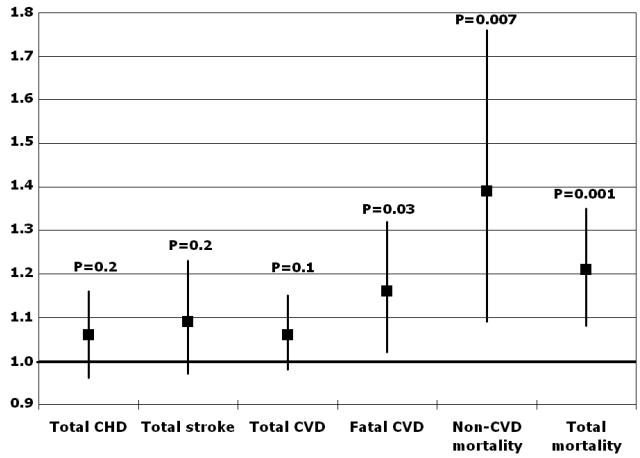
Figure 8. Hazard ratios (95% confidence intervals) for fatal/non-fatal CHD, stroke and CVD, and non-CVD and total mortality, in 7,822 patients on insulin based therapy (alone or combined with OHAs) compared with 6,687 patients treated with OHAs alone, followed for 6 years.
Adjustment as in Table 10 and also for history of CVD and history of congestive heart failure before baseline.

GENERAL DISCUSSION

MAIN FINDINGS

These large observational studies on patients with diabetes in everyday clinical practice show a slow improvement in glycaemic control and risk factors in type 1 diabetes. They also demonstrate progressively increasing risks of CHD and CVD in type 1 diabetes with higher levels of HbA1c, independently of other traditional risk factors, over a period of 5 years. Those with a mean baseline HbA1c of 7.2% showed considerably reduced risks of CHD and CVD compared with those with a level of 9.0%. In type 2 diabetes, increasing risks of CHD and CVD were also seen with higher HbA1c levels over a period of 6 years, but no increase in risk was seen for those with low HbA1c levels, with short or long duration of diabetes, with or without a history of CVD, or when treated with insulin or OHA. Both overweight and obesity independently increased the risk of CHD and CVD in patients with type 2 diabetes. Before discussing the results and clinical implications in detail some methodological considerations will be addressed.

METHODOLOGICAL CONSIDERATIONS

Basic epidemiology

Well-conducted, randomized controlled trials (RCTs) are regarded as the gold standard in evidence-based medicine, and provide the highest level of evidence (82, 128). When evaluating the effects of treatment, RCTs and systematic reviews are the most reliable methods: they have high internal validity but, due to strict inclusion and exclusion criteria, the external validity and generalizability are sometimes limited (129). There are also situations in which experimental studies are not possible, appropriate, practical or ethical (130). Observational studies are often used to investigate the occurrence of health-related events (disease, complications, death, survival) in a given population over a certain period of time, and can reveal associations that may or may not be causal. It is therefore important to analyse the strengths and weaknesses of observational studies and to establish how well they agree with previous scientific knowledge (116). Observational studies have generally been regarded as providing evidence of lower value than RCTs (82, 128). However, well-performed and clearly reported observational studies can provide important information from clinical practice, contributing external validity to previous findings (131). According to two reviews comparing the results of observational studies and RCTs, observational studies did not in general overestimate the risk (132, 133).

In 2007, the STROBE (Strengthening the Reporting in Observational studies in Epidemiology) statement initiative was published providing a checklist, discussion and explanations, with the aim of improving reporting and underlining the clinical importance of well-performed observational studies (116). STROBE emphasizes the importance of clearly reporting the intention of the study, the methods used, and the

findings, to help the reader judge both the internal validity and the generalizability of the observational study (116). The internal validity of a study is a question of whether the study measures what it intended to measure, while external validity relates to how well the results apply to other groups of patients, i.e. generalizability (134). When designing and interpreting epidemiological studies one must be aware of the random and systematic errors that can affect the internal and external validity. Random errors decrease as the size of the study population increases, whereas a systematic error will remain unchanged and could distort the results even in large studies (135).

Random errors
Random errors, or chance findings, are addressed in statistical methods to determine whether the result is likely to be true, or due to chance. Statistical significance does not address the magnitude of the relative risk found in the study, only the likelihood that it would have resulted from chance alone, if there were no real association (135). The null hypothesis states that there is no relation between exposure and outcome (relative risk 1.0). In calculating the p-value we answer the question: What is the probability of finding a difference, at least of this size, when there is really none? When p=0.05, this means that the probability of finding a difference, even when there is none is 5%. Random error can also be described using confidence intervals, where the width reflects the random error (135). The main strengths of the present studies are the large number of patients included and the large number of outcome events, which should minimize the random errors.

Systematic errors
Systematic errors, also called bias, usually refer to selection bias, information bias and confounding. Information bias can be divided into measurement errors and misclassification (differential or non-differential) (134).

Selection bias
Selection bias means that the groups studied are not comparable, for instance the controls have not been properly selected, or exposed and unexposed subjects have been selected in different ways (134). This kind of selection bias effects the internal validity, and is of special importance in case-control studies and when comparing several cross-sectional surveys. As the cross-sectional survey described here (Study I) does not include all patients with type 1 diabetes in Sweden, this could lead to selection bias. It cannot be ruled out that reporting units more interested in diabetes care and quality assurance were those participating from the start of the NDR. However, this is likely to be a smaller problem concerning type 1 diabetes, since almost all type 1 diabetes patients in Sweden have their regular check up at hospital outpatient clinics and most hospital outpatient clinics participated from the start of the register, and in 2004 more than 95% of the clinics reported to the NDR. In the cohort studies with a prospective design (Studies II-IV), all available patient data in the NDR meeting the inclusion criteria were included with the aim of following up all these patients with regard to

outcome, and selection bias should thus be a minor problem.

In the cohort Studies II, III and IV only those with complete data on baseline variables were included, which could have led to a selection bias. However, the ability to adjust for confounding baseline variables in the regression models was improved. One of the strengths of the NDR database is the amount of registered clinical characteristics, often lacking in other register-based studies.

Information bias – Measurement errors and misclassification
Measurement errors cannot be ruled out, as data from the participating centres are collected according to local practices and may vary in accuracy. Guidelines, reasonably well-known to the reporting units, are available in order to minimize errors, corrections are made to prevent registration of extreme data values, and direct transferral of data from patient record databases is being increasingly used. Laboratory analyses are carried out at local laboratories, but there is a nationwide programme to calibrate HbA1c levels to a standard. A validation study of the data in the NDR has shown accuracy in reporting from hospital clinics, and validation processes in primary healthcare centres are ongoing.

In Studies II-IV, the outcome events were retrieved by linkage to the Swedish Cause of Death Register and the Hospital Discharge Register. The accuracy of cardiovascular diagnoses in these registers is generally regarded as high, and validation studies have shown approximately 95% correct diagnosis for myocardial infarction and stroke, and about 80% for congestive heart failure, compared with hospital records (118-121). As all the outcome events were retrieved in the same manor, misclassification can be regarded as non-differential and less likely to affect the risk estimates.

In the studies on type 1 diabetes, an epidemiological definition of type 1 diabetes, including patients with age of onset <30 years, on insulin only, was used (mean onset age 15 years), similar to the definition used in EURODIAB PCS (70), and this should exclude patients with type 2 diabetes reasonably well. Concerning the epidemiological definition of type 2 diabetes used here (diet only, oral agents only, or onset of diabetes at age 40 or above when treated with insulin only or combined with oral agents), should exclude most type 1 diabetic patients. However, antibody measurements are not reported in the NDR, and it is possible that a small number of the type 2 diabetic patients may have been misclassified latent autoimmune diabetes in adult life (LADA) patients.

Confounding
A confounding factor must be associated with disease independent of exposure; must be associated with exposure independent of the disease; and not be an intermediate in the causal pathway between exposure and disease. Controlling for confounding factors is essential in epidemiological observational studies. Restriction or matching proce-

dures may be used or, in the analysis phase, stratification, by dividing the confounding factor into different strata, or adjusting for confounding factors in multivariable analysis (135).

In the present studies confounding were considered by adjusting for known confounding variables in the multivariable analysis. Stratification was also used in some of the studies, for example, shorter and longer duration of diabetes, history or not of previous CVD, and type of treatment. One of the unique advantages of the NDR is the number of clinical characteristics and laboratory values recorded at least once a year, making it possible to adjust for important confounding factors. However, residual confounding of unmeasured or unknown factors possibly linked to the outcome must be considered when interpreting the results. Blood lipid values were not recorded before 2002 in the NDR, and thus a major limitation of the two studies with their baseline in 1997-1998 is the lack of this information, which is known to be an important confounder when assessing CVD risk. Instead lipid-lowering medication (mostly statins) was used as a marker of hyperlipidaemia. Excellent agreement between predicted risk and observed risk during follow-up has been demonstrated when using lipid-lowering drug therapy instead of blood lipid levels, among other risk factors in a multivariate analysis to develop a model for risk prediction of CVD (136).

No information was available in the NDR on the frequency or severity of hypoglycaemia, nor detailed information on the types of insulin or oral hypoglycaemic agents used, or their doses in 1997-1998, thus no adjustment could be made for these factors. Both the STROBE statement (116) and Rosén and colleagues (137) have pointed out the importance of addressing confounding factors due to differences in socioeconomic factors. This was not done in the present studies and, although important, it is likely to be a smaller problem in Sweden than in many other countries, given the social structure and the nationwide availability of healthcare and social services, and should not have influenced the results in a significant way.

DISCUSSION OF MAIN FINDINGS
Risk factor control and treatment targets in type 1 diabetes
A slow improvement in glycaemia and risk factor control, apart from a small increase in BMI from 1997 to 2004, was seen in the cross-sectional study. The number of patients reaching the treatment target of HbA1c <7% increased from 17% in 1997 to 21% in 2004. The number reaching HbA1c <8% increased from 49% to 56% in 2004, while significantly fewer, less than 20%, had a level of HbA1c ≥9%. The most evident change was the increase in the proportion with LDL cholesterol <2.5 mmol/L, from 38% in 2002 to 48% in 2004, combined with the increasing use of lipid-lowering medication. Furthermore, the proportion with blood pressure ≤130/80 mmHg increased from 58% to 61%, in parallel with an increase in antihypertensive medication. A high proportion of diabetes patients were found to have hypertension in our study (46%), as also reported by others (138-140), and the increased use of antihypertensive medica-

tion from 23% to 34%, probably also indicates the increased use of ACE inhibitors for the treatment of microalbuminuria alone, reflecting adherence to guidelines. Eye and foot status were checked in almost all patients in 2004. Taken together, these findings represent measures for improved risk factor control and diabetes care.

Only a few, small surveys of the clinical care of type 1 diabetes are available in the literature (141, 142). Reports from NHANES, with samples selected to be representative of the US diabetes population, including considerably more patients with type 2 than type 1 diabetes with a higher mean age of about 56 years, and only about 30% being treated with insulin, show improvement in diabetes care during the period 1988-94 to 1999-2002; more patients receiving annual lipid- and microalbuminuria testing, eye and foot examination, and influenza vaccination (143). It was also reported that 63% of patients reached HbA1c <8%, 34% reached LDL cholesterol <2.6 mmol/L and 60% blood pressure <140/90 mmHg at follow-up in 1999-2002. The number of smokers remained high, about 20% (63). Recent NHANES data on glycaemic control show encouraging improvements in HbA1c, from a mean value of 7.8% in 1999-2000 to 7.2% in 2003-2004; while 76% reached the target level HbA1c <8% (144). Improved blood pressure and blood lipid levels have also been reported (145).

In the present study, the achievement in 2004 of targets for blood pressure ≤130/80 mmHg in 61% of all patients, HbA1c <8% in 56%, and LDL cholesterol <2.5 mmol/L in about half of the patients, in a survey reasonably representative of all Swedish patients with type 1 diabetes, is encouraging for the care of type 1 diabetes in Sweden. However, concerning lifestyle factors, the frequency of smoking was high in middle age (14-17%), and higher in younger women (15-16%) than in younger men (9%) and further improvement is warranted. The present study also showed that long-term successful glycaemic control (HbA1c <7.3% in 1997 and in 2004) was independently predicted by low BMI, not smoking and the absence of microalbuminuria at baseline.

Glycaemic control and cardiovascular risk in type 1 diabetes
Study II, on 7454 younger and middle-aged patients (20-65 years) with type 1 diabetes, shows a strong independent association between HbA1c and both CHD and CVD. Each 1%-unit increase in baseline HbA1c or updated mean HbA1c was associated with risk increases of 31-34% for CHD and 26-32% for CVD, after adjustment for age, sex, diabetes duration and traditional cardiovascular risk factors. These increases in risk remained significant, but were slightly attenuated to 28-30% (for CHD) and 22-27% (for CVD) after adjustment also for albuminuria. Fully adjusted 5-year event rates of CHD and CVD increased progressively with higher HbA1c levels. Most previous comparable epidemiological studies on type 1 diabetes have not demonstrated any clear association between glycaemic control and risk of CHD (70, 96-98).

Prior to the present study, the DCCT/EDIC study has been the only study providing convincing evidence of a relation between glycaemic control and risk of CVD in type

1 diabetes (93). Patients were randomized to intensive or standard treatment and followed for 6 years during the DCCT (86), and in the subsequent observational EDIC study of 1182 patients, two groups with mean HbA1c levels of 7.4% and 9.1% were followed for another 11 years regarding CVD events. The EDIC study demonstrated a 42% lower relative risk of any first-incident cardiovascular disease, and a 57% reduction in fatal/non-fatal CVD in the former intensively treated group. In the present study, the group with a mean HbA1c level of 7.2% at baseline showed relative risk reductions of 41% for CHD and 37% for CVD, compared with the group with a mean HbA1c level of 9.0%, when followed for 5 years. The present study, on data from 2002 to 2007, thus provides strong support for the results of the EDIC study conducted from 1994 to 2005.

Glycaemic control and cardiovascular disease in type 2 diabetes
The present study on type 2 diabetic patients in everyday clinical practice, 18% of which had a history of CVD, showed increased relative risks of CHD (11-13%), stroke (8-9%), CVD (10-11%) and total mortality (9-10%) per 1%-unit increase in both baseline and mean updated HbA1c levels during 6 years of follow-up, after adjustment for age, sex and cardiovascular risk factors. These findings are in line with the results of most previous observational studies. A large study conducted in New Zealand, in which patients were followed for 2.4 years, demonstrated an 8% higher risk of both fatal/non-fatal MI and CVD with 1%-unit increase in baseline HbA1c (101). An observational UKPDS study, where patients were followed for 10 years, demonstrated a 14-16% higher risk of MI and stroke per 1%-unit increase in updated mean HbA1c values during the study (100).

Apart form the UKPDS study of overweight patients, in which patients treated with metformin showed a 39% lower risk of MI (p=0.01) and a 36% lower risk of death from any cause (p=0.01), compared with conventional treatment (mean HbA1c 7.4% versus 7.9%) (146), no intervention studies have successfully shown a reduced risk of CVD in intensively treated patients. The UKPDS intervention study showed a non-significant relative risk reduction of 16% (p=0.052) for fatal/non-fatal MI with a mean HbA1c level of 7.0% versus 7.9% (61). The three large RCTs, ACCORD, ADVANCE and VATD (88, 106, 107), including patients with longer diabetes duration, of which about one third had previous CVD, found no reduction in CVD risk in intensively treated patients followed for 3½ to 5 years. A 22% increased risk of total mortality in the intensively treated group was seen in the ACCORD study, and the trial was stopped early. A meta-analysis of these 4 studies showed a 9% reduction in risk of major CVD events (HbA1c difference of 0.9%), mainly driven by a 15% lower risk of non-fatal MI (147). A meta-analysis by Ray and colleagues also including the Proactive study (Prospective pioglitazone clinical trial in macrovascular events) (148), revealed a similar reduction in risk of non-fatal MI and CVD in the intensively treated patients. No effect of intensive glucose control on stroke or total mortality was seen in either of the meta-analysis studies. In the present study (Study IV), comparable with regard to

previous CVD, mean age and follow-up time, patients with baseline HbA1c levels of 6.0-6.9% (mean 6.5%) had a 20% lower relative risk of fatal/non-fatal CHD, and a 16% lower risk of fatal/non-fatal CVD than patients with HbA1c levels of 7.0-7.9% (mean 7.5%).

Concerns have been raised following the ACCORD study (106) and after an observational study based on the UK GPRD (108) as to whether lowering the HbA1c level increases mortality in patients with type 2 diabetes. In the study by Currie and colleagues, 27,000 patients on OHA therapy and 20,000 patients on insulin based therapy (alone or combined with OHA therapy) at baseline were identified during the period 1986–2008 and followed for 5 years. The results showed an increased risk of all-cause mortality and progression to non-fatal CVD at both lower and higher HbA1c levels; the lowest risk being seen for patients with an HbA1c level of 7.5% (108). In contrast, in the present study, the adjusted 6-year event rates for CHD, stroke, CVD and total mortality increased progressively with increasing HbA1c level, and there were no J-shaped risk curves in the total cohort, in patients with shorter or longer diabetes duration, in those with or without previous CVD, or in those treated with insulin or OHAs. The UK GPRD study demonstrated a HR of 1.49 (1.39-1.59) for total mortality in patients on insulin treatment at baseline, compared with oral treatment. In the present study, the increased risk of total mortality in the insulin-treated group was caused almost exclusively by the highly significant increased risk of non-CVD mortality in this group, whereas the increased risk of fatal CVD was only weakly significant. These findings were interpreted as being a risk related to a higher frequency of co-morbidity in patients receiving insulin, and not the insulin per se. In addition, we found no association between HbA1c and non-CVD mortality, while this was not analysed in the UK GPRD study. The two studies are comparable with regard to mean age, HbA1c level, unadjusted mortality rates and follow-up duration. Currie and colleagues concluded that if their results were confirmed, guidelines may require revision to include a minimum HbA1c value (108), but such conclusions were not supported by the results of the present study.

BMI, overweight and obesity and CVD risk in type 2 diabetes
The associations between the risk of CVD and overweight and obesity were investigated as overweight and obesity are highly prevalent in type 2 diabetes, and the findings in previous studies in this area have been inconsistent. Study III included patients aged from 30 to 75, with no previous CVD, and clearly showed a 15% increased risk of fatal/non-fatal CHD, 11% for stroke, 13% for CVD and a 27% increased risk of total mortality with a 5-unit increase in baseline BMI, adjusted for age, sex, type of hypoglycaemic treatment, diabetes duration and smoking. These risks were attenuated, but remained significant (except for stroke) when also adjusting for HbA1c, systolic blood pressure, antihypertensive drugs, lipid-lowering drugs, and microalbuminuria.

The WHO has addressed the issue of adjusting for confounding factors with regard to BMI and CVD risk, suggesting that in order not to underestimate the risk, factors closely related to BMI, such as hypertension, hyperlipidaemia, hyperglycaemia and microalbuminuria, should not be considered confounding and adjusted for (23). We believe the completely adjusted model presented here contributes valuable information, indicating that about half of the increased risk of CHD and CVD with higher BMI was mediated through factors other than hypertension, HbA1c, hyperlipidaemia and microalbuminuria. Other variables, for example, low-grade inflammation, endothelial dysfunction and disturbed fibrinolysis, are probably involved in the causal pathway between overweight and obesity and increased risk of CHD (149, 150), and other factors linked to insulin resistance and lipotoxicity, related to atherosclerosis could also be involved (151). In the present study adjustment was made using lipid-lowering medication as a proxy for dyslipidaemia, at baseline (1997-98), most likely representing high LDL cholesterol levels, whereas factors related to insulin resistance, for instance low HDL cholesterol and high triglycerides, were not accounted for in this model.

The INTERHEART case-control study showed similar results in the general population, with a significant HR 1.10 (95% CI 1.07-1.13) for MI per 1 SD increase in BMI (1 SD=4.15), when adjusted for age, sex and region, but no increase in risk when adjusting for all other INTERHEART risk factors. In that study, BMI was found to be a weaker risk factor than WHR and waist circumference with corresponding HRs of 1.37 (1.34-1.41) for WHR and 1.19 (1.16-1.22) for waist circumference (152). These risks were still significantly increased after adjustment for all other INTERHEART risk factors. Although other measures of obesity can certainly provide important information, BMI as a measure of general adiposity is a strong predictor of mortality in the general population (57, 58). In a recent large collaborative analysis of prospective studies, the rate of mortality among the general population was found to be lowest for BMI=22.5-25 kg/m^2; above 25 kg/m^2 there was a 30% increase in all-cause mortality, with a 40% increase in vascular mortality, for every 5-unit increase in BMI (153). The present study shows that not only obesity, but also overweight, increased the risk of fatal/non-fatal CHD and CVD in patients with type 2 diabetes, and also that obesity, but not overweight, increased the risk of total mortality and CVD mortality.

The present study of the effects of weight change in almost 5000 patients with BMI=25-40 kg/m^2 at baseline showed that those who gained most weight during the study (median BMI change + 3.8 kg/m^2) had a roughly 2-fold increased risk of CHD compared with those who gained less or lost weight. A previous study in the US on 4,970 overweight and obese type 2 diabetes patients, followed from 1959 to 1972) showed a 28% reduction in CVD mortality as a result of intentional weight loss, and a U-shaped curve with maximum risk reduction at a weight loss of 10-15% of initial weight (154). Results from the Nurses' Health Study in the US showed that weight increase before the diagnosis of diabetes was associated with an increased risk of CHD

in women, whereas weight change after the diagnosis of diabetes was not (65). Weight change with regard to diabetes is a complex matter, as weight loss could reflect poorly controlled diabetes, and weight gain could be attributable to pharmacological treatment to improve metabolic control (155). Many hypoglycaemic agents, for example insulin, sulphonylurea and thiazolidinedione, are often associated with weight gain, but not to the same extent with all treatment strategies, as exemplified by the differences between the ACCORD and ADVANCE trials (156). Patients in the intensively treated group in the ACCORD study gained, on average, 3.5 kg and 28% gained >10 kg, compared with 0.4 kg and 14% >10 kg in the standard treatment group (106). No weight change was seen in either the intensively treated group or the standard treatment group in the ADVANCE study (88).

CLINICAL IMPLICATIONS

An important finding of the research presented in this thesis regarding glycaemic control and CVD risk in type 1 diabetes is the strong support of the finding in the DCCT/EDIC study that glycaemic control aimed at a treatment target of HbA1c <7% is related to a reduced risk of CVD (93), but the present finding was based on a five times larger cohort of patients with type 1 diabetes in everyday modern clinical practice. The present research also provides new information by showing that higher levels of HbA1c also increase the risk of fatal/non-fatal CHD independently of other CVD risk factors, including lipid levels and albuminuria. Patients with both shorter and longer durations of their illness seemed to benefit from lower HbA1c levels, and no increase in the risk of CHD or CVD was observed at low HbA1c levels.

In type 1 diabetes, the absolute risks, i.e. a 5-year mean event rate of 2% for CHD and 2.4% for CVD, are lower than those observed in type 2 diabetes, where the 6-year event rates were 17% for CHD and 24% for CVD. However, it is important to keep in mind that the mean age of the type 1 diabetic patients was at least 20 years lower than in the study on patients with type 2 diabetes. Taken together, these findings emphasize the role of HbA1c as a strong independent risk factor in type 1 diabetes.

Concerning type 2 diabetes, the results of this work confirmed those of other observational studies in that higher HbA1c levels led to an increased risk of CHD, stroke, CVD and total mortality. We found progressively higher risks, estimated as 6-year event rates for all fatal/non-fatal outcomes, fatal events and total mortality, with increasing HbA1c. No J-shaped risk curves were seen, indicting no increase in the risk at low levels of HbA1c, in contrast to findings in the UK GPRD study (108). Although the present study was not a randomized trial analysing strict control aimed at lowering the HbA1c levels, this observational study based on everyday clinical practice in patients 30 to 79 years old shows significant reductions in the risk of fatal/non-fatal CHD and CVD during six years' follow-up, when comparing a group with a mean baseline HbA1c level of 6.5% with a group with a 1%-unit higher mean HbA1c. Patients with longer duration of diabetes and previous CVD had higher absolute risks,

while patients with both shorter and longer duration of diabetes (more than 7 years), those with or without previous CVD, as well as those on insulin or oral drug treatment, had a lower risk of CVD at lower HbA1c levels.

Observational long-term follow-up studies of type 1 diabetes patients in the DCCT (93) and type 2 diabetes patients in the UKPDS (157), show maintained reduction in risk of microvascular complications with intensive treatment and routine treatment, and also significant reductions in the risk of CVD in the formerly intensively treated group compared with the group receiving standard treatment. This reduction in the risk of CVD, more than 10 years after the intensive intervention was stopped, and the similar HbA1c levels during the observational follow-up period, suggest a metabolic memory or legacy effect of lowering the glucose level (93, 157). These findings, indicating that early glycaemic control in patients with short duration of the illness, may provide benefits in the form of risk reduction several years later, are not contradictory to ours, but in the present studies patients with both longer and shorter duration of diabetes had a lower risk at lower HbA1c levels.

Following the findings in the DCCT/EDIC and the UKPDS, and the findings presented in the recent ACCORD, ADVANCE and VATD trials, a position statement from the ADA still recommends a general HbA1c target level of <7%, but also points out that goals should be individualized based on the duration of diabetes, known CVD and advanced microvascular complications, limited life expectancy and unawareness of hypoglycaemia (82, 158). The new national Swedish treatment guidelines, also recommends a general HbA1c target level of <7% based on individualized evaluation, with a less stringent goal for patients with advanced microvascular and macrovascular complications, limited life expectancy and increased risk of hypoglycaemia (84, 109). The current findings support these Swedish guidelines.

Comparison of glycaemia with other CVD risk factors
The ongoing debate on the risks and benefits of glycaemic control is discussed in a recent editorial in Diabetologia by Yudkin and Gale (159). They argue that since both interventional and observational studies show that lowering the HbA1c level reduces the risk of CVD less than lowering the LDL cholesterol level and blood pressure, it may be better to focus on blood pressure and cholesterol targets in many patients, as these are more easily achieved (159). There is reduction in risk of CHD of about 20-30% per 1 mmol/L lower cholesterol level, a 20-25% lower risk with a 10/5 mm Hg decrease in blood pressure, and 10% lower risk per 1%-unit HbA1c (147, 160-163).

However, this argument can be reversed, showing that lowering blood pressure, glucose and cholesterol levels all contribute to a reduction in the risk of CVD, which underscores the importance of addressing them all by lifestyle changes and pharmacological treatment. Both hyperglycaemia and insulin resistance are linked to accelerated atherosclerosis through increased inflammation, oxidative stress and endothelial dysfunction,

and promoting thrombosis. Furthermore, hyperglycaemia changes the properties of lipoproteins through glycation, making them more atherogenic, as well as increasing the risk of microvascular disease, which is also a risk factor for CVD and mortality (27, 29). It is evident that it is worthwhile to strive towards optimal glycaemic control for the individual patient. Yudkin and Gale clearly state that poor glycaemic control, with HbA1c levels above 8% should definitely be avoided, but also point out that the benefits associated with HbA1c levels below 7.5% are reduced in patients with greater age and shorter life expectancy (159). In the present study of type 2 diabetes, an upper age limit of 79 years was applied to the patients included and the relative risk reductions of 20% for CHD and 16% for CVD with mean HbA1c levels of 6.5% versus 7.5%.

Study III demonstrates that avoiding overweight and obesity is beneficial for adult patients with type 2 diabetes with regard to CVD risk, and that an increase in BMI was associated with a higher CVD risk than stable or decreasing BMI during the 6-year study period. However, it cannot be concluded from these findings that intentionally loosing weight will reduce the risk. The Look AHEAD (Action for health in diabetes) trial in the US is an ongoing study with the primary objective of establishing whether intentional weight loss through intensive lifestyle interventions can reduce CVD risk in type 2 diabetes (164). Over 5000 overweight or obese patients, aged 55-74, were assigned either intensive lifestyle changes, including diet and physical activity, or standard care. At baseline, 14% reported a history of CVD, 88% were on hypoglycaemic medication, including 15% on insulin, 75% were being treated with antihypertensive medication, 50% with lipid-lowering medication, and 85% were obese. The results after one year were presented in 2007. The group subjected to intensive lifestyle changes had lost more weight than the other group (8.6% vs. 0.7%). This was accompanied by a larger reduction in waist circumference, better glycaemic and blood pressure control, and lower lipid levels, compared with the standard group, despite the fact that they were taking significantly less medication (164). It will be interesting to see whether these changes are maintained over time, and whether the CVD risk is affected. The best measure of obesity can be debated, but the most important aspect is to avoid or minimize obesity in patients with type 2 diabetes. Waist circumference is reported more frequently in the NDR in recent years (around 50% in 2009), as is physical activity (5-level scale from never to daily), and these measures can be analysed in the future.

Improvement makes a difference
In the Steno-2 study multifactorial risk factor intervention including both intensive pharmacological and lifestyle changes in patients with type 2 diabetes, showed a 50% reduction in the relative risk of CVD and microvascular complications after 8 years, and in total mortality after 13 years, despite the fact that the study stopped after 8 years (80, 81).

The Linköping Diabetes Complication Study has shown that modern treatment of type 1 diabetes patients could reduce the frequencies of severe retinopathy and neph-

ropathy after 25 years, from 47% to 24% (165). Declining rates of nephropathy have also been reported from Steno in Denmark (166) and in the Pittsburgh EDC study (167). New results from a study combining the DCCT cohort with a comparable cohort from the Pittsburgh EDC study show declining cumulative incidence rates of microvascular complications and lower CVD rates in the formerly intensively treated group of the DCCT study than in the conventionally treated group in the DCCT study and the EDC study, when followed for 30 years. The rates of proliferative retinopathy, nephropathy and CVD were 50%, 25% and 14%, respectively, in the formerly standard-treated DCCT group; very similar to the rates in the EDC study reflecting standard treatment, while the corresponding rate in the formerly intensively treated DCCT group were 14%, 9% and 9%, respectively (168). The researchers conducting these studies concluded that the improvement, showing fewer long-term complications, is the result of modern diabetes care.

During follow-up in these studies, the aim of treatment was to control the glycaemic level, and to treat hypertension and albuminuria. Clinical guidelines today advocate multifactorial risk factor control in both type 1 and type 2 diabetes. The effects of more recent treatment strategies, focusing also on reducing blood lipid levels by the increased use of lipid-lowering medication, and lifestyle changes including giving up smoking, should be evaluated in the future.

FUTURE PERSPECTIVES

The challenge now is to further implement evidence-based knowledge in diabetes care. We also need to expand our knowledge on what really matters to our patients, also by collecting and analysing patient-reported outcome measures (PROMs). Observational studies in clinical settings are important tools to evaluate the outcome of different treatment strategies, both old and new, in clinical practice, as they provide answers to questions such as: Are there differences between different treatment strategies with regard to outcome? Which patients benefit the most from a certain treatment? Are there differences in gender perspectives? and Are we considering the right outcome measure? Outcomes are not only micro- and macrovascular complications, renal impairment and cancer, but also the health and well-being of the individual patient.

The aim of the Swedish NDR is to continuously improve diabetes care in Sweden. Today, 70% of all patients with diabetes are reported to the NDR, and the number is increasing steadily. New variables have been added as a result of the knowledge gained and requests from clinicians using the register in their daily treatment of patients. Important clinical information has been registered in recent years, such as physical activity and waist circumference since 2004, and hypoglycaemia since 2009. Future possibilities also include database linkage to other databases, for instance, the pharmaceutical register, which contains full information on dispensed prescriptions since 2005. Studies on ways of including patient-reported outcome measures in the NDR are ongoing.

CONCLUSIONS

• The Swedish NDR is a unique source of information on patients with diabetes in everyday clinical practice, and an important tool for improving diabetes care.

• Well-performed and clearly reported observational studies are important complements to randomized controlled trials, and can contribute important knowledge in the clinical practice setting.

• A slow improvement was seen in glycaemic control and risk factor control in patients with type 1 diabetes from 1997 to 2004, as well as increasing adherence to guidelines. However, further improvement is warranted. Successful glycaemic control was independently predicted by low BMI, not smoking and the absence of microalbuminuria.

• In patients with type 1 diabetes, higher HbA1c was found to be independently associated with increased risk of CHD and CVD when followed for 5 years. This emphasizes the role of HbA1c as a strong independent risk factor in type 1 diabetes.

• In type 2 diabetes, increasing risks of CHD and CVD were seen in patients with higher HbA1c levels, while no risk increase was seen in those with low HbA1c levels, regardless of the duration of diabetes, previous CVD history, or treatment (with insulin or OHA). HbA1c levels lower than 7% were associated with a lower risk of CVD, providing support for current treatment guidelines.

• Higher BMI, overweight and obesity independently increased the risk of CHD and CVD in patients with type 2 diabetes, providing additional evidence that overweight and obesity should be counteracted in type 2 diabetes.

SAMMANFATTNING PÅ SVENSKA

Bakgrund
Diabetes är en sjukdom som kännetecknas av högt blodsocker till följd av brist på insulin eller minskad känslighet för insulin. Typ 1 diabetes är en autoimmun sjukdom som leder till att insulinproduktionen upphör. Den drabbar ofta unga individer. Typ 2 diabetes debuterar vanligtvis efter 40 års ålder och är ofta kopplad till andra sjukdomar som övervikt, fetma och högt blodtryck. I Sverige finns idag ca 365,000 personer med diabetes, av dessa har 10% typ 1 diabetes och 90% typ 2 diabetes.

Hjärt- kärlsjukdom är den vanligaste dödsorsaken i Sverige och står för ca 40% av den totala dödligheten. Under de senaste decennierna har förekomst av hjärt- kärlsjukdom närmast halverats till följd av både minskat insjuknande och ökad överlevnad efter hjärtinfarkt och stroke. Trots denna förbättring har patienter med diabetes en klart ökad risk för hjärt- kärlsjukdom och död jämfört med befolkningen i stort. Vikten av att påverka riskfaktorer, t.ex. genom rökstopp, behandling av högt blodtryck och blodfetter, är central, vilket understryks av nationella riktlinjer.

När det gäller blodsockerkontroll vet vi att intensiv behandling av blodsockret genom lägre blodsockernivåer (HbA1c värdet är ett mått på blodsockernivån under de senaste 2 månaderna), på sikt minskar risken för skador på de små kärlen i ögon, njurar och nerver, men huruvida lägre blodsocker också minskar risken för hjärt- kärlsjukdom, är inte lika välbelagt vid typ 1 diabetes och omdiskuterat vid typ 2 diabetes. Övervikt och fetma är kända riskfaktorer för hjärt- kärlsjukdom i hela befolkningen, men även om övervikt/fetma är vanligt vid typ 2 diabetes, är sambandet mellan övervikt/fetma och hjärt-kärlsjukdom inte lika tydligt vid typ 2 diabetes.

Syfte
Målen med de här studierna har dels varit att beskriva den kliniska bilden och riskfaktorkontrollen hos patienter med typ 1 diabetes, samt att se hur väl nationella behandlingsmål uppnås och dels att studera sambandet mellan blodsockerkontroll och hjärt-kärlsjukdom vid både typ 1 diabetes och typ 2 diabetes. Målet var även att studera samband mellan övervikt och fetma och hjärt-kärlsjukdom vid typ 2 diabetes.

Metod och resultat
Dessa observationsstudier omfattar patienter med diabetes som finns rapporterade i Nationella diabetesregistret (NDR). NDR är ett nationellt kvalitetsregister som startade 1996 med syfte att utveckla och säkra diabetesvårdens kvalitet. Antalet registrerade patienter har successivt ökat till över 260,000 2009, vilket motsvarar ca 70 % av alla personer med diabetes i Sverige.

Hos patienter med typ 1 diabetes har riskfaktorkontrollen av HbA1c, blodtryck och

blodfetter förbättrats över tid, i kombination med ökad användning av blodtrycks- och blodfettssänkande läkemedel. Under 2004 nådde ca hälften av patienterna målen: blodtryck ≤130/80 mm Hg, HbA1c <8% (7% Mono-S) och LDL <2,5 mmol/L. Rökning har totalt sett minskat men 2004 var unga kvinnor den grupp som rökte mest (16% jämfört med 9% bland jämnåriga män).

7454 patienter med typ 1 diabetes följdes från 2002/03-2007 avseende hjärt-kärlsjukdom. För varje enhet högre HbA1c ökade risken för en hjärt- kärlhändelse med 30% under uppföljningstiden, efter att hänsyn tagits till andra faktorer som skulle kunna påverka hjärt- kärlsjukdom. Studien visade att patienter med HbA1c 5-7.9% (medeltal 7.2%) vid studiestart hade 40% lägre risk för att drabbas av hjärt-kärlhändelse jämfört med patienter med HbA1c 8-11.9% (medeltal 9.0%).

I de två studierna av patienter med typ 2 diabetes följdes 13,087 respektive 18,336 patienter under 6 år från 1997/98 till 2003. Övervikt och fetma ökade risken för hjärt-kärlsjukdom med 24-44% jämfört med normalvikt. Av studien framgår att högre HbA1c ökade risken för hjärtkärlsjukdom men studien visade ingen ökad risk vid låga HbA1c nivåer, inte heller hos patienter med längre diabetesduration eller tidigare hjärt- kärlsjuklighet. HbA1c under 7% var förenat med lägre risk för hjärtkärlsjukdom.

Slutsats
Avhandlingsarbetet baserat på data från patienter i daglig klinisk verksamhet visar på förbättrad riskfaktorkontroll vid typ 1 diabetes och visar att lägre blodsocker ger en lägre risk för hjärt-kärlsjukdom både vid typ 1 och typ 2 diabetes. Studierna ger stöd åt nuvarande behandlings rekommendationer vad gäller blodsockerkontroll. Dessutom understryks att övervikt och fetma bör undvikas vid typ 2 diabetes.

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REFERENCES

1.   Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998 Jul;15(7):539-53.
2.   World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia : report of a WHO/IDF consultaion. WHO Document Production Services, Geneva, Switzerland wwwwhoint/diabetes/publications/en/. 2006.
3.   IDF. http://www.diabetesatlas.org/content/what-is-diabetes (last accessed 10 October 2010).
4.   Daneman D. Type 1 diabetes. Lancet. 2006 Mar 11;367(9513):847-58.
5.   Borchers AT, Uibo R, Gershwin ME. The geoepidemiology of type 1 diabetes. Autoimmun Rev. 2010 Mar;9(5):A355-65.
6.   Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. Lancet. 2005 Apr 9-15;365(9467):1333-46.
7.   Defronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009 Apr;58(4):773-95.
8.   Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004 May;27(5):1047-53.
9.   Forouhi NG, Merrick D, Goyder E, Ferguson BA, Abbas J, Lachowycz K, et al. Diabetes prevalence in England, 2001--estimates from an epidemiological model. Diabet Med. 2006 Feb;23(2):189-97.
10.   Lipscombe LL, Hux JE. Trends in diabetes prevalence, incidence, and mortality in Ontario, Canada 1995-2005: a population-based study. Lancet. 2007 Mar 3;369(9563):750-6.
11.   Carstensen B, Kristensen JK, Ottosen P, Borch-Johnsen K. The Danish National Diabetes Register: trends in incidence, prevalence and mortality. Diabetologia. 2008 Dec;51(12):2187-96.
12.   Eliasson M, Lindahl B, Lundberg V, Stegmayr B. No increase in the prevalence of known diabetes between 1986 and 1999 in subjects 25-64 years of age in northern Sweden. Diabet Med. 2002 Oct;19(10):874-80.
13.   Jansson SP, Andersson DK, Svardsudd K. Prevalence and incidence rate of diabetes mellitus in a Swedish community during 30 years of follow-up. Diabetologia. 2007 Apr;50(4):703-10.
14.   Berger B, Stenstrom G, Chang YF, Sundkvist G. The prevalence of diabetes in a Swedish population of 280,411 inhabitants. A report from the Skaraborg Diabetes Registry. Diabetes Care. 1998 Apr;21(4):546-8.
15.   Berger B, Stenstrom G, Sundkvist G. Incidence, prevalence, and mortality of diabetes in a large population. A report from the Skaraborg Diabetes Registry. Diabetes Care. 1999 May;22(5):773-8.
16.   Ringborg A, Lindgren P, Martinell M, Yin DD, Schon S, Stalhammar J. Prevalence and incidence of Type 2 diabetes and its complications 1996-2003--estimates from a Swedish population-based study. Diabet Med. 2008 Oct;25(10):1178-86.
17.   Folkhälsorapport 2009. The National Board of Health and Welfare. http://www.socialstyrelsen.se/publikationer2009/2009-126-71 (last accessed 10 October 2010). 2009
18.   Incidence and trends of childhood Type 1 diabetes worldwide 1990-1999. Diabet Med. 2006 Aug;23(8):857-66.
19.   Patterson CC, Dahlquist GG, Gyurus E, Green A, Soltesz G. Incidence trends for

childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. Lancet. 2009 Jun 13;373(9680):2027-33.

20. Pundziute-Lycka A, Dahlquist G, Nystrom L, Arnqvist H, Bjork E, Blohme G, et al. The incidence of Type I diabetes has not increased but shifted to a younger age at diagnosis in the 0-34 years group in Sweden 1983-1998. Diabetologia. 2002 Jun;45(6):783-91.

21. Thunander M, Petersson C, Jonzon K, Fornander J, Ossiansson B, Torn C, et al. Incidence of type 1 and type 2 diabetes in adults and children in Kronoberg, Sweden. Diabetes Res Clin Pract. 2008 Nov;82(2):247-55.

22. Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. Jama. 2003 Jan 1;289(1):76-9.

23. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser. 2000;894:i-xii, 1-253.

24. Statistics Sweden. Background Facts, Population and Welfare Statistics 2010:4, Changes in the Life Conditions Survey 2006–2008. http://www.scb.se/LE0101 (last accessed 10 October 2010). 2010.

25. Libby P. Inflammation in atherosclerosis. Nature. 2002 Dec 19-26;420(6917):868-74.

26. Libby P, Theroux P. Pathophysiology of coronary artery disease. Circulation. 2005 Jun 28;111(25):3481-8.

27. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes. 2005 Jun;54(6):1615-25.

28. Retnakaran R, Zinman B. Type 1 diabetes, hyperglycaemia, and the heart. Lancet. 2008 May 24;371(9626):1790-9.

29. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. JAMA. 2002 May 15;287(19):2570-81.

30. Jansson PA. Endothelial dysfunction in insulin resistance and type 2 diabetes. J Intern Med. 2007 Aug;262(2):173-83.

31. Bjorck L, Rosengren A, Bennett K, Lappas G, Capewell S. Modelling the decreasing coronary heart disease mortality in Sweden between 1986 and 2002. Eur Heart J. 2009 May;30(9):1046-56.

32. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. N Engl J Med. 2007 Jun 7;356(23):2388-98.

33. Unal B, Critchley JA, Capewell S. Modelling the decline in coronary heart disease deaths in England and Wales, 1981-2000: comparing contributions from primary prevention and secondary prevention. BMJ. 2005 Sep 17;331(7517):614.

34. Tunstall-Pedoe H, Kuulasmaa K, Mahonen M, Tolonen H, Ruokokoski E, Amouyel P. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. Lancet. 1999 May 8;353(9164):1547-57.

35. Tunstall-Pedoe H, Vanuzzo D, Hobbs M, Mahonen M, Cepaitis Z, Kuulasmaa K, et al. Estimation of contribution of changes in coronary care to improving survival, event rates, and coronary heart disease mortality across the WHO MONICA Project populations. Lancet. 2000 Feb 26;355(9205):688-700.

36. Fox CS, Coady S, Sorlie PD, Levy D, Meigs JB, D'Agostino RB, Sr., et al. Trends in cardiovascular complications of diabetes. JAMA. 2004 Nov 24;292(20):2495-9.

37.   Hu FB, Stampfer MJ, Solomon CG, Liu S, Willett WC, Speizer FE, et al. The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women: 20 years of follow-up. Arch Intern Med. 2001 Jul 23;161(14):1717-23.

38.   Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. Bmj. 2006 Jan 14;332(7533):73-8.

39.   Mulnier HE, Seaman HE, Raleigh VS, Soedamah-Muthu SS, Colhoun HM, Lawrenson RA. Mortality in people with type 2 diabetes in the UK. Diabet Med. 2006 May;23(5):516-21.

40.   Lotufo PA, Gaziano JM, Chae CU, Ajani UA, Moreno-John G, Buring JE, et al. Diabetes and all-cause and coronary heart disease mortality among US male physicians. Arch Intern Med. 2001 Jan 22;161(2):242-7.

41.   Krolewski AS, Kosinski EJ, Warram JH, Leland OS, Busick EJ, Asmal AC, et al. Magnitude and determinants of coronary artery disease in juvenile-onset, insulin-dependent diabetes mellitus. Am J Cardiol. 1987 Apr 1;59(8):750-5.

42.   Laing SP, Swerdlow AJ, Slater SD, Burden AC, Morris A, Waugh NR, et al. Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. Diabetologia. 2003 Jun;46(6):760-5.

43.   Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010 Jun 26;375(9733):2215-22.

44.   Soedamah-Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM. All-cause mortality rates in patients with type 1 diabetes mellitus compared with a non-diabetic population from the UK general practice research database, 1992-1999. Diabetologia. 2006 Apr;49(4):660-6.

45.   Soedamah-Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM. High risk of cardiovascular disease in patients with type 1 diabetes in the U.K.: a cohort study using the general practice research database. Diabetes Care. 2006 Apr;29(4):798-804.

46.   Gregg EW, Gu Q, Cheng YJ, Narayan KM, Cowie CC. Mortality trends in men and women with diabetes, 1971 to 2000. Ann Intern Med. 2007 Aug 7;147(3):149-55.

47.   Dale AC, Vatten LJ, Nilsen TI, Midthjell K, Wiseth R. Secular decline in mortality from coronary heart disease in adults with diabetes mellitus: cohort study. BMJ. 2008;337:a236.

48.   Eliasson M, Talback M, Rosen M. Improved survival in both men and women with diabetes between 1980 and 2004--a cohort study in Sweden. Cardiovasc Diabetol. 2008;7:32.

49.   Norhammar A, Lindback J, Ryden L, Wallentin L, Stenestrand U. Improved but still high short- and long-term mortality rates after myocardial infarction in patients with diabetes mellitus: a time-trend report from the Swedish Register of Information and Knowledge about Swedish Heart Intensive Care Admission. Heart. 2007 Dec;93(12):1577-83.

50.   Haffner SM, Lehto S, Ronnemaa T, Pyorala 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 Jul 23;339(4):229-34.

51.   Juutilainen A, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Type 2 diabetes as a "coronary heart disease equivalent": an 18-year prospective population-based study in Finnish subjects. Diabetes Care. 2005 Dec;28(12):2901-7.

52.   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 Feb;16(2):434-44.

53. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTER-HEART study): case-control study. Lancet. 2004 Sep 11-17;364(9438):937-52.

54. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet. 2010 Jul 10;376(9735):112-23.

55. Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, Ballard-Barbash R, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. N Engl J Med. 2006 Aug 24;355(8):763-78.

56. Bogers RP, Bemelmans WJ, Hoogenveen RT, Boshuizen HC, Woodward M, Knekt P, et al. Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels: a meta-analysis of 21 cohort studies including more than 300 000 persons. Arch Intern Med. 2007 Sep 10;167(16):1720-8.

57. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW, Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med. 1999 Oct 7;341(15):1097-105.

58. Jee SH, Sull JW, Park J, Lee SY, Ohrr H, Guallar E, et al. Body-mass index and mortality in Korean men and women. N Engl J Med. 2006 Aug 24;355(8):779-87.

59. Jonsson S, Hedblad B, Engstrom G, Nilsson P, Berglund G, Janzon L. Influence of obesity on cardiovascular risk. Twenty-three-year follow-up of 22,025 men from an urban Swedish population. Int J Obes Relat Metab Disord. 2002 Aug;26(8):1046-53.

60. Turner RC, Millns H, Neil HA, Stratton IM, Manley SE, Matthews DR, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). BMJ. 1998 Mar 14;316(7134):823-8.

61. UKPDS. 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 Sep 12;352(9131):837-53.

62. Ridderstrale M, Gudbjornsdottir S, Eliasson B, Nilsson PM, Cederholm J. Obesity and cardiovascular risk factors in type 2 diabetes: results from the Swedish National Diabetes Register. J Intern Med. 2006 Mar;259(3):314-22.

63. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. Jama. 2004 Jan 21;291(3):335-42.

64. Chaturvedi N, Fuller JH. Mortality risk by body weight and weight change in people with NIDDM. The WHO Multinational Study of Vascular Disease in Diabetes. Diabetes Care. 1995 Jun;18(6):766-74.

65. Cho E, Manson JE, Stampfer MJ, Solomon CG, Colditz GA, Speizer FE, et al. A prospective study of obesity and risk of coronary heart disease among diabetic women. Diabetes Care. 2002 Jul;25(7):1142-8.

66. Thomas F, Bean K, Pannier B, Oppert JM, Guize L, Benetos A. Cardiovascular mortality in overweight subjects: the key role of associated risk factors. Hypertension. 2005 Oct;46(4):654-9.

67. Zoppini G, Verlato G, Leuzinger C, Zamboni C, Brun E, Bonora E, et al. Body mass index and the risk of mortality in type II diabetic patients from Verona. Int J Obes Relat Metab Disord. 2003 Feb;27(2):281-5.

68. Avogaro A, Giorda C, Maggini M, Mannucci E, Raschetti R, Lombardo F, et al. Incidence of coronary heart disease in type 2 diabetic men and women: impact of microvascular complications, treatment, and geographic location. Diabetes Care. 2007 May;30(5):1241-7.

69.   Rossing P, Hougaard P, Borch-Johnsen K, Parving HH. Predictors of mortality in insulin dependent diabetes: 10 year observational follow up study. BMJ. 1996 Sep 28;313(7060):779-84.

70.   Soedamah-Muthu SS, Chaturvedi N, Toeller M, Ferriss B, Reboldi P, Michel G, et al. Risk factors for coronary heart disease in type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study. Diabetes Care. 2004 Feb;27(2):530-7.

71.   Soedamah-Muthu SS, Chaturvedi N, Witte DR, Stevens LK, Porta M, Fuller JH. Relationship between risk factors and mortality in type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study (PCS). Diabetes Care. 2008 Jul;31(7):1360-6.

72.   Tuomilehto J, Borch-Johnsen K, Molarius A, Forsen T, Rastenyte D, Sarti C, et al. Incidence of cardiovascular disease in Type 1 (insulin-dependent) diabetic subjects with and without diabetic nephropathy in Finland. Diabetologia. 1998 Jul;41(7):784-90.

73.   Forrest KY, Becker DJ, Kuller LH, Wolfson SK, Orchard TJ. Are predictors of coronary heart disease and lower-extremity arterial disease in type 1 diabetes the same? A prospective study. Atherosclerosis. 2000 Jan;148(1):159-69.

74.   Patel A, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet. 2007 Sep 8;370(9590):829-40.

75.   Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. Bmj. 1998 Sep 12;317(7160):703-13.

76.   HOPE. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. Lancet. 2000 Jan 22;355(9200):253-9.

77.   Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004 Aug 21-27;364(9435):685-96.

78.   Pyorala 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 Apr;20(4):614-20.

79.   Collins R, Armitage J, Parish S, Sleigh P, Peto R. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet. 2003 Jun 14;361(9374):2005-16.

80.   Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med. 2003 Jan 30;348(5):383-93.

81.   Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med. 2008 Feb 7;358(6):580-91.

82.   Standards of medical care in diabetes--2010. Diabetes Care. 2010 Jan;33 Suppl 1:S11-61.

83.   Ryden L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, de Boer MJ, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur Heart J. 2007

Jan;28(1):88-136.

84.	SBU. Intensiv glukossänkande behandling vid diabetes. En systematisk litteraturöversikt. Stockholm: Statens beredning för medicinsk utvärdering (SBU); 2010. SBU-rapport nr 196. ISBN 978-97-85413-32-4.

 85.	Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EA, et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. Diabetes Care. 2009 Jan;32(1):187-92.

86.	DCCT. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med. 1993 Sep 30;329(14):977-86.

87.	Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. N Engl J Med. 1993 Jul 29;329(5):304-9.

88.	Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008 Jun 12;358(24):2560-72.

89.	Goldstein DE, Little RR, Lorenz RA, Malone JI, Nathan DM, Peterson CM. Tests of glycemia in diabetes. Diabetes Care. 2004 Jan;27 Suppl 1:S91-3.

90.	Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ. Translating the A1C assay into estimated average glucose values. Diabetes Care. 2008 Aug;31(8):1473-8.

91.	Hoelzel W, Weykamp C, Jeppsson JO, Miedema K, Barr JR, Goodall I, et al. IFCC reference system for measurement of hemoglobin A1c in human blood and the national standardization schemes in the United States, Japan, and Sweden: a method-comparison study. Clin Chem. 2004 Jan;50(1):166-74.

92.	Consensus statement on the worldwide standardisation of the HbA1c measurement. Diabetologia. 2007 Oct;50(10):2042-3.

93.	Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005 Dec 22;353(25):2643-53.

94.	Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. Am J Cardiol. 1995 May 1;75(14):894-903.

95.	Lehto S, Ronnemaa T, Pyorala K, Laakso M. Poor glycemic control predicts coronary heart disease events in patients with type 1 diabetes without nephropathy. Arterioscler Thromb Vasc Biol. 1999 Apr;19(4):1014-9.

96.	Orchard TJ, Olson JC, Erbey JR, Williams K, Forrest KY, Smithline Kinder L, et al. Insulin resistance-related factors, but not glycemia, predict coronary artery disease in type 1 diabetes: 10-year follow-up data from the Pittsburgh Epidemiology of Diabetes Complications Study. Diabetes Care. 2003 May;26(5):1374-9.

97.	Klein BE, Klein R, McBride PE, Cruickshanks KJ, Palta M, Knudtson MD, et al. Cardiovascular disease, mortality, and retinal microvascular characteristics in type 1 diabetes: Wisconsin epidemiologic study of diabetic retinopathy. Arch Intern Med. 2004 Sep 27;164(17):1917-24.

98.	Prince CT, Becker DJ, Costacou T, Miller RG, Orchard TJ. Changes in glycaemic control and risk of coronary artery disease in type 1 diabetes mellitus: findings from the Pittsburgh Epidemiology of Diabetes Complications Study (EDC). Diabetologia. 2007 Nov;50(11):2280-

8.

99.   Gerstein HC, Pogue J, Mann JF, Lonn E, Dagenais GR, McQueen M, et al. The relationship between dysglycaemia and cardiovascular and renal risk in diabetic and non-diabetic participants in the HOPE study: a prospective epidemiological analysis. Diabetologia. 2005 Sep;48(9):1749-55.

100.   Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. Bmj. 2000 Aug 12;321(7258):405-12.

101.   Elley CR, Kenealy T, Robinson E, Drury PL. Glycated haemoglobin and cardiovascular outcomes in people with Type 2 diabetes: a large prospective cohort study. Diabet Med. 2008 Nov;25(11):1295-301.

102.   Brewer N, Wright CS, Travier N, Cunningham CW, Hornell J, Pearce N, et al. A New Zealand linkage study examining the associations between A1C concentration and mortality. Diabetes Care. 2008 Jun;31(6):1144-9.

103.   Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. Ann Intern Med. 2004 Sep 21;141(6):413-20.

104.   Myint PK, Sinha S, Wareham NJ, Bingham SA, Luben RN, Welch AA, et al. Glycated hemoglobin and risk of stroke in people without known diabetes in the European Prospective Investigation into Cancer (EPIC)-Norfolk prospective population study: a threshold relationship? Stroke. 2007 Feb;38(2):271-5.

105.   Selvin E, Coresh J, Golden SH, Brancati FL, Folsom AR, Steffes MW. Glycemic control and coronary heart disease risk in persons with and without diabetes: the atherosclerosis risk in communities study. Arch Intern Med. 2005 Sep 12;165(16):1910-6.

106.   Gerstein HC, Miller ME, Byington RP, Goff DC, Jr., Bigger JT, Buse JB, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008 Jun 12;358(24):2545-59.

107.   Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009 Jan 8;360(2):129-39.

108.   Currie CJ, Peters JR, Tynan A, Evans M, Heine RJ, Bracco OL, et al. Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study. Lancet. 2010 Feb 6;375(9713):481-9.

109.   Nationella riktlinjer för diabetesvården 2010. http://www.socialstyrelsen.se/publikationer2010/2010-2-2 (last accessed 10 October 2010). 2010.

110.   Gudbjornsdottir S, Cederholm J, Nilsson PM, Eliasson B. The National Diabetes Register in Sweden: an implementation of the St. Vincent Declaration for Quality Improvement in Diabetes Care. Diabetes Care. 2003 Apr;26(4):1270-6.

111.   Diabetes care and research in Europe: the Saint Vincent declaration. Diabet Med. 1990 May;7(4):360.

112.   Gudbjornsdottir S. Nationella diabetesregistres Årsrapport 2005. 2005.

113.   Grimes DA, Schulz KF. An overview of clinical research: the lay of the land. Lancet. 2002 Jan 5;359(9300):57-61.

114.   Grimes DA, Schulz KF. Cohort studies: marching towards outcomes. Lancet. 2002 Jan 26;359(9303):341-5.

115.   Schulz KF, Grimes DA. Case-control studies: research in reverse. Lancet. 2002 Feb 2;359(9304):431-4.

116.   Vandenbroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ,

et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Ann Intern Med. 2007 Oct 16;147(8):W163-94.

117.   Bain SC, Gill GV, Dyer PH, Jones AF, Murphy M, Jones KE, et al. Characteristics of Type 1 diabetes of over 50 years duration (the Golden Years Cohort). Diabet Med. 2003 Oct;20(10):808-11.

118.   Hammar N, Alfredsson L, Rosen M, Spetz CL, Kahan T, Ysberg AS. A national record linkage to study acute myocardial infarction incidence and case fatality in Sweden. Int J Epidemiol. 2001 Oct;30 Suppl 1:S30-4.

119.   Ingelsson E, Arnlov J, Sundstrom J, Lind L. The validity of a diagnosis of heart failure in a hospital discharge register. Eur J Heart Fail. 2005 Aug;7(5):787-91.

120.   Lindblad U, Rastam L, Ranstam J, Peterson M. Validity of register data on acute myocardial infarction and acute stroke: the Skaraborg Hypertension Project. Scand J Soc Med. 1993 Mar;21(1):3-9.

121.   Merlo J, Lindblad U, Pessah-Rasmussen H, Hedblad B, Rastam J, Isacsson SO, et al. Comparison of different procedures to identify probable cases of myocardial infarction and stroke in two Swedish prospective cohort studies using local and national routine registers. Eur J Epidemiol. 2000 Mar;16(3):235-43.

122.   Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972 Jun;18(6):499-502.

123.   Clark TG, Bradburn MJ, Love SB, Altman DG. Survival analysis part I: basic concepts and first analyses. Br J Cancer. 2003 Jul 21;89(2):232-8.

124.   Bradburn MJ, Clark TG, Love SB, Altman DG. Survival analysis part II: multivariate data analysis--an introduction to concepts and methods. Br J Cancer. 2003 Aug 4;89(3):431-6.

125.   Heinzl H, Kaider A. Gaining more flexibility in Cox proportional hazards regression models with cubic spline functions. Comput Methods Programs Biomed. 1997 Nov;54(3):201-8.

126.   UCLA. UCLA – Stat computing: http://www.ats.ucla.edu/stat/sas/faq/test_proportionality.htm (last accessed 10 October 2010).

127.   Liu L FS, Barton B. Fitting Cox Model Using PROC PHREG and Beyond in SAS. SAS Global Forum 2009. 2009(paper 236):1-10.

128.   Hannan EL. Randomized clinical trials and observational studies: guidelines for assessing respective strengths and limitations. JACC Cardiovasc Interv. 2008 Jun;1(3):211-7.

129.   Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". Lancet. 2005 Jan 1-7;365(9453):82-93.

130.   Black N. Why we need observational studies to evaluate the effectiveness of health care. BMJ. 1996 May 11;312(7040):1215-8.

131.   Yang W, Zilov A, Soewondo P, Bech OM, Sekkal F, Home PD. Observational studies: going beyond the boundaries of randomized controlled trials. Diabetes Res Clin Pract. 2010 May;88 Suppl 1:S3-9.

132.   Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. N Engl J Med. 2000 Jun 22;342(25):1878-86.

133.   Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med. 2000 Jun 22;342(25):1887-92.

134.   Grimes DA, Schulz KF. Bias and causal associations in observational research. Lancet. 2002 Jan 19;359(9302):248-52.

135.   Rothman K. Epidemiology - an introduction. Oxford University Press. 2002.

136.   Cederholm J, Eeg-Olofsson K, Eliasson B, Zethelius B, Nilsson PM, Gudbjornsdottir S. Risk prediction of cardiovascular disease in type 2 diabetes: a risk equation from the Swedish National Diabetes Register. Diabetes Care. 2008 Oct;31(10):2038-43.

137.   Rosen M, Axelsson S, Lindblom J. [Don't throw out the observation studies with the bath-water. Assess their quality instead]. Lakartidningen. 2008 Nov 5-11;105(45):3191-4.

138.   Collado-Mesa F, Colhoun HM, Stevens LK, Boavida J, Ferriss JB, Karamanos B, et al. Prevalence and management of hypertension in type 1 diabetes mellitus in Europe: the EU-RODIAB IDDM Complications Study. Diabet Med. 1999 Jan;16(1):41-8.

139.   Zgibor JC, Wilson RR, Orchard TJ. Has control of hypercholesterolemia and hypertension in type 1 diabetes improved over time? Diabetes Care. 2005 Mar;28(3):521-6.

140.   Maahs DM, Kinney GL, Wadwa P, Snell-Bergeon JK, Dabelea D, Hokanson J, et al. Hypertension prevalence, awareness, treatment, and control in an adult type 1 diabetes population and a comparable general population. Diabetes Care. 2005 Feb;28(2):301-6.

141.   Coppell KJ, Anderson K, Williams S, Manning P, Mann J. Evaluation of diabetes care in the Otago region using a diabetes register, 1998-2003. Diabetes Res Clin Pract. 2006 Mar;71(3):345-52.

142.   Jacobs ML, Elte JW, van Ouwerkerk BM, Janssens EN, Schop C, Knoop JA, et al. Effect of BMI, insulin dose and number of injections on glycaemic control in insulin-using diabetic patients. Studygroup Diabetes Rijnmond (SDR). Neth J Med. 1997 Apr;50(4):153-9.

143.   Saaddine JB, Cadwell B, Gregg EW, Engelgau MM, Vinicor F, Imperatore G, et al. Improvements in diabetes processes of care and intermediate outcomes: United States, 1988-2002. Ann Intern Med. 2006 Apr 4;144(7):465-74.

144.   Hoerger TJ, Segel JE, Gregg EW, Saaddine JB. Is glycemic control improving in U.S. adults? Diabetes Care. 2008 Jan;31(1):81-6.

145.   Hoerger TJ, Zhang P, Segel JE, Gregg EW, Narayan KM, Hicks KA. Improvements in risk factor control among persons with diabetes in the United States: evidence and implications for remaining life expectancy. Diabetes Res Clin Pract. 2009 Dec;86(3):225-32.

146.   Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):854-65.

147.   Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia. 2009 Nov;52(11):2288-98.

148.   Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005 Oct 8;366(9493):1279-89.

149.   Berg AH, Scherer PE. Adipose tissue, inflammation, and cardiovascular disease. Circ Res. 2005 May 13;96(9):939-49.

150.   Rahman S, Rahman T, Ismail AA, Rashid AR. Diabetes-associated macrovasculopathy: pathophysiology and pathogenesis. Diabetes Obes Metab. 2007 Nov;9(6):767-80.

151.   DeFronzo RA. Insulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: the missing links. The Claude Bernard Lecture 2009. Diabetologia. 2010 Jul;53(7):1270-87.

152.   Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, et al. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. Lancet. 2005 Nov 5;366(9497):1640-9.

153.   Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, et al. Body-

mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009 Mar 28;373(9669):1083-96.

154.   Williamson DF, Thompson TJ, Thun M, Flanders D, Pamuk E, Byers T. Intentional weight loss and mortality among overweight individuals with diabetes. Diabetes Care. 2000 Oct;23(10):1499-504.

155.   Hermansen K, Mortensen LS. Bodyweight changes associated with antihyperglycaemic agents in type 2 diabetes mellitus. Drug Saf. 2007;30(12):1127-42.

156.   Bergenstal RM, Bailey CJ, Kendall DM. Type 2 diabetes: assessing the relative risks and benefits of glucose-lowering medications. Am J Med. 2010;123(4):374 e 9 -18.

157.   Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008 Oct 9;359(15):1577-89.

158.   Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EA, et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. Circulation. 2009 Jan 20;119(2):351-7.

159.   Yudkin JS, Richter B, Gale EA. Intensified glucose lowering in type 2 diabetes: time for a reappraisal. Diabetologia. 2010;53(10):2079-85.

160.   Yudkin JS, Richter B. Intensive glucose control and cardiovascular outcomes. Lancet. 2009 Aug 15;374(9689):522; author reply 4.

161.   Turnbull F, Neal B, Algert C, Chalmers J, Chapman N, Cutler J, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch Intern Med. 2005 Jun 27;165(12):1410-9.

162.   Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med. 2004 Sep 21;141(6):421-31.

163.   Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008 Jan 12;371(9607):117-25.

164.   Pi-Sunyer X, Blackburn G, Brancati FL, Bray GA, Bright R, Clark JM, et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. Diabetes Care. 2007 Jun;30(6):1374-83.

165.   Nordwall M, Bojestig M, Arnqvist HJ, Ludvigsson J. Declining incidence of severe retinopathy and persisting decrease of nephropathy in an unselected population of Type 1 diabetes-the Linkoping Diabetes Complications Study. Diabetologia. 2004 Jul;47(7):1266-72.

166.   Hovind P, Tarnow L, Rossing K, Rossing P, Eising S, Larsen N, et al. Decreasing incidence of severe diabetic microangiopathy in type 1 diabetes. Diabetes Care. 2003 Apr;26(4):1258-64.

167.   Pambianco G, Costacou T, Ellis D, Becker DJ, Klein R, Orchard TJ. The 30-year natural history of type 1 diabetes complications: the pittsburgh epidemiology of diabetes complications study experience. Diabetes. 2006 May;55(5):1463-9.

168.   Nathan DM, Zinman B, Cleary PA, Backlund JY, Genuth S, Miller R, et al. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983-2005). Arch Intern Med. 2009 Jul 27;169(14):1307-16.

ERRATA

Study I

In the abstract under results the sentence written … only 61.3% reached the blood pressure goal of <130/80 mm Hg in 2004. Should read … only 39.3% reached the blood pressure goal of <130/80 mm Hg in 2004 (61.3% reached ≤130/80 mm Hg).

Table I, first column BP <140/85 mm Hg (%) should read BP ≤140/85 mmHg (%).

Table I, second and third column. Numbers of patients given in parentheses at different ages are incorrect. Should read 1997: aged <30 years, women (1231); aged <30 years, men (1424); aged 30-59 years (6129) and aged >60 years (613). 2004: aged <30 years, women (1188); aged <30 years, men (1430); aged 30-59 years (8178) and aged >60 years (1408).