Treatment of Cardiovascular Risk Factors in Type 2 Diabetes
- Time Trends and Clinical Practice

Eva Fhärm
Borde man inte kunna begripa människorna, sade Linda?
Jo, sade han. Det vore det allra bästa.

Torgny Lindgren, Pölsan, 2004
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ORIGINAl PAPERS
ABSTRACT

Objectives

Patients with type 2 diabetes are at much greater risk of developing cardiovascular diseases (CVD), including coronary heart disease (CHD), compared to non-diabetics. The lowering of glucose, blood pressure, and plasma lipid levels has been shown to reduce CHD risk, and treatment goals for these risk factors are now part of clinical practice guidelines. However, the incidence and outcome of CHD in diabetic patients does not show the same favourable trend as in the general population.

Thus, the overall aim of the thesis was to investigate how the treatment goals for CVD risk factors contained in the national guidelines for diabetes care were reflected in clinical practice, and to explore factors that might influence the remaining high incidence of CHD in the type 2 diabetes population.

Research designs and results

I. The effectiveness of the introduction of treatment goals for dyslipidaemia was evaluated in a retrospective observational population-based cross-sectional study of 971 diabetic patients participating in the Västerbotten Intervention Programme (VIP) 1995–2004. There was a stronger trend of decrease in cholesterol levels among patients with diabetes compared to the non-diabetic population in 2000–2004. Increased use of lipid-lowering agents influenced the trend in diabetic patients, even though only 25.3% received lipid-lowering treatment after the introduction of the new guidelines.

II. The experiences of general practitioners relating to treatment practice for type 2 diabetes with specific focus on the prevention of cardiovascular disease were explored in a focus group study. The overall theme was ‘dilemmas’ in GPs’ treatment practice for patients with type 2 diabetes. Five main dilemma categories were identified. First, GPs were hesitant about labelling a person who feels healthy as ill. Second, as regards communicating a diabetes diagnosis and its consequences, GPs were unsure as to whether patients should be frightened or comforted. Third, GPs experienced uncertainty in their role: should they take responsibility for the care or not? Fourth, GPs expressed concern over a conflict between lifestyle changes and drug treatment. Fifth, the GPs described difficulties when attempting to translate science into reality.

III. Screening for microvascular and coronary heart disease according to national guidelines was evaluated in a cross-sectional study of 201 screening-detected patients with type 2 diabetes 1.5±0.7 years after diagnosis. A larger proportion of diabetic patients was screened for nephropathy and
retinopathy than for CHD. Twenty-three percent of the patients had minor or major ECG abnormalities, but ECG findings seemed to have little or no impact on CHD prevention using lipid-lowering medication and ASA. A clinical history of CHD correlated with a larger proportion of patients receiving secondary prevention.

IV. Time trends relating to the achievement of treatment goals and 10-year CHD risk at three years of diabetes duration were studied in 19,382 patients with type 2 diabetes without CHD, who were reported by primary health care sources in the National Diabetes Register in 2003–2008. National treatment goals for glycaemia, blood pressure, total cholesterol, and LDL cholesterol were achieved in 78.4%, 65.5%, 55.6%, and 61.0%, respectively, of the diabetic patients in 2008 following a trend of improved results in 2003–2008. Absolute 10-year risk of CHD increased between year of diagnosis and follow up in a studied subgroup while modifiable risk decreased.

Conclusions

The introduction of treatment goals for dyslipidemia in Swedish national guidelines in 1999 were reflected in lowered cholesterol levels in people with type 2 diabetes. Since the introduction of the guidelines, an increasing number of diabetic patients are treated in accordance with guidelines. A remaining microvascular focus on the patients together with the revealed dilemmas within the GP’s consultation with diabetic patients might negatively influence the remaining high incidence of CHD in the type 2 diabetes population. Lipid levels, blood pressure and smoking are targets for further improvements.

Key words: diabetes mellitus, cardiovascular disease, effectiveness, epidemiology, guideline adherence, primary health care, risk factor


I arbete II intervjuades 14 erfarna allmänlärare från nio vårdcentraler i fokusgrupper om sina erfarenheter av diabetesvård med särskilt fokus på förebyggande av hjärtkärlsjukdom hos personer med typ-2-diabetes. I analysen av intervjuerna framkom ett tema, ”dilemma”, där fem kategorier identifierades. För det första, läkarna tvekade inför att beteckna en person som kände sig frisk som varandes sjuk. För det andra, när det gällde att kommunicera en diabetesdiagnos och dess konsekvenser; skulle patienten skrämmas eller tröstas? För det tredje, läkarna upplevde en osäkerhet i sin roll; skulle de ta ansvar för vården eller inte? För det fjärde, läkarna upplevde en konflikt mellan livsstilsförändring och läkemedelsbehandling. För det femte, läkarna beskrev svårigheter att integrera vetenskap i klinisk praxis.

I arbete III studerades om 201 patienter med typ-2-diabetes, som diagnosti- cerats när de deltog i VHU, hade screenats för kranst-kärlssjukdom i samma utsträckning som för mikrovaskulära diabeteskomplikationer, dvs ögonbottenförändringar, njurskada och perifer nervskada. Vi fann att 1,5 år efter diagnos hade fler screenats för ögonbottenförändringar och njurskada än för kranst-kärlssjukdom. EKG-förändringar tydande på ökad hjärt-kärlrisk fanns hos 23% av patienterna, men föreföll inte påverka användandet av förebyggande behandling med blodfettssänkande läkemedel eller acetylsalicylsyra. En klinisk kranst-kärlssdiagnos, å andra sidan, var korrelerad till ökad användning av förebyggande behandling.
I arbete IV studerades tidstrender i riskfaktornivåer, uppnåelse av behandlingsmål för riskfaktorer för hjärt-kärlsjukdom samt påverkan på beräknad 10-årsrisk för hjärtinfarkt och plötslig död till följd av hjärtinfarkt. Hos 19382 patienter, 30-70 år gamla, med typ-2-diabetes sedan tre år tillbaka som rapporterats i Nationella Diabetesregistret (NDR) i primärvården 2003–2008 och som inte hade känd kranskärlssjukdom fann vi att 78.4%, 65.5%, 55.6%, och 61.0% nådde målen för vartdera blodsocker, blodtryck, totalkolesterol och LDL-kolesterol 2008. Under hela perioden skedde en sänkning av riskfaktornivåerna och detta medförde också en sänkning av den absoluta 10-årsrisken för hjärtinfarkt och plötslig död till följd av hjärtinfarkt. I en subgrupp av typ-2-diabetespatienter med rapporterade värden såväl diagnosåret som efter i genomsnitt 2,6 år hade den absoluta risken ökat mellan mätpunkterna, medan den modifierbara risken sänkts.

# Abbreviations

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<th>Abbreviation</th>
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<tr>
<td>ADA</td>
<td>American Diabetes Association</td>
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<tr>
<td>ASA</td>
<td>Acetyl salicylic acid</td>
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<td>ACR</td>
<td>Albumine creatinine ratio</td>
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<td>BMI</td>
<td>Body mass index</td>
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<td>CHD</td>
<td>Coronary heart disease</td>
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<td>CI</td>
<td>Confidence interval</td>
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<td>CVD</td>
<td>Cardiovascular disease</td>
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<td>ECG</td>
<td>Electrocardiogram</td>
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<td>GP</td>
<td>General Practitioner</td>
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<td>HDL</td>
<td>High-density lipoprotein</td>
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<td>LDL</td>
<td>Low-density lipoprotein</td>
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<td>LLD</td>
<td>Lipid lowering drug</td>
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<td>MI</td>
<td>Myocardial infarction</td>
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<td>MONICA</td>
<td>Multinational MONItoring of trends and determinants in CArdiovascular disease, a WHO project</td>
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<tr>
<td>OGTT</td>
<td>Oral glucose tolerance test</td>
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<td>OHA</td>
<td>Oral hypoglycaemic agent</td>
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<td>NDR</td>
<td>National Diabetes Register (Sweden)</td>
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<td>NHANES</td>
<td>National Health And Nutrition Examinations Surveys (USA)</td>
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<td>SD</td>
<td>Standard deviation</td>
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<td>UKPDS</td>
<td>United Kingdom Prospective Diabetes Study</td>
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<td>VIP</td>
<td>Västerbotten Intervention Programme</td>
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<td>WHO</td>
<td>World Health Organisation</td>
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This thesis is based on the following papers, referred to in the text by their Roman numerals:


Papers I and II are reprinted by permission of SAGE Publications and Oxford University Press, respectively.
When I first started my training to become a general practitioner in the 80s my impression of a typical patient with diabetes was an elderly woman with foot- ulcers, overweight, high blood pressure, and coronary heart disease. All of these medical problems were considered severe and incurable by the consultants at the hospital. An air of hopelessness was associated with a diabetes diagnosis and intervention was not on the cards.

The picture has changed during my years as a GP and so have the problems. A diabetes diagnosis is nowadays seldom the answer for a patient with typical symptoms – more often it is a laboratory diagnosis for an asymptomatic patient. This raises new challenges for both patient and doctor in understanding and communicating consequences and necessary actions. What remains is the obvious high prevalence of cardiovascular disease in patients with diabetes.

As I began my research, my aim was to understand diabetes care in real life, especially the prevention of cardiovascular complications. My hypothesis was that cardiovascular prevention was problematic in clinical practice due to a number of reasons, i.e. doctors’ and patients’ understanding of the condition, all the things to consider and deal with inside a consultation, and possibly other unknown factors.

My belief is that shared knowledge between all concerned is the basis of good decisions. This thesis is the result of my own desire to increase my knowledge. I hope that at least some of the results will be discussed among health care professionals and people with diabetes and thus increase the basis for good decision-making.
INTRODUCTION

Type 2 diabetes mellitus

Epidemiology

The prevalence of diabetes, including all subtypes, is on the rise worldwide and in 2000 it was estimated that there were 171 million people with diabetes on earth, which corresponds to a prevalence of 2.8% for all age-groups. In 2030 it is estimated that the prevalence will have risen to 4.4% [1]. The prevalence of type 2 diabetes increases with age and the worldwide increase in the proportion of people ≥ 65 years of age alone will result in escalated diabetes prevalence [1]. It has also been suggested that population growth, improved survival in patients with diabetes, urbanization, increased obesity, and physical inactivity are contributing to the upsurge in the number of people with diabetes in the world [2, 3]. An increased diabetes incidence in the US was demonstrated in the Framingham and San Antonio Heart Study cohorts [2, 4] but some question whether or not there has been a true increase of diabetes incidence worldwide [3, 5].

Type 2 diabetes is the predominant type of diabetes and it is responsible for 90–95% of all diabetes in adults [6]. Seemingly, some populations are more susceptible and develop type 2 diabetes more easily. People of African or Asian ethnicity have a higher prevalence of type 2 diabetes than people of other ethnicity [7, 8]. Diabetes is more common in men < 60 years of age, but more common in women at older ages, resulting in more women than men with diabetes in the world [1]. In people at lower socio-economic levels, with shorter education, overweight, physical inactivity, and smoking, the prevalence of type 2 diabetes is increased [9]. Diabetes is also on the increase among children, due to a rise in child obesity combined with genetic susceptibility [10, 11].

Most studies since the 1980s have reported increased diabetes prevalence in Sweden as well, and the main contributing factors are the increase in the proportion of elderly and demonstrated improved survival [9, 12, 13]. An increased prevalence of type 2 diabetes was also found in Laxå in central Sweden between 1972 and 1988 using a case finding procedure involving 85% of a population of about 8500 [14]. However, during the period 1988 to 2001 there was no rise in diabetes prevalence [6]. In order to enable early diagnoses, screening for diabetes has been carried out in some parts of Sweden. In adults, a variation in diabetes prevalence rates has been identified. In the population-based survey MONICA, which includes oral glucose tolerance tests (OGTTs), in northern Sweden 1986–1999, the prevalence of diabetes was 5.7% in men and 4.6% in women aged 25–64 [15]. In the VIP, which is a population-based intervention programme that also includes OGTT, the diabetes prevalence in people aged 30–60 years was 5% in men and 3.9% in women [16]. Somewhat lower diabetes prevalence in people 35–79 years (M/F 4.5%/4.4%) was reported from Laxå using mainly blood glucose as the screening method [6]. However, no increase in the incidence of diabetes in Sweden as a whole was found [6, 12, 15].
Definition and diagnosis
Diabetes mellitus is a heterogeneous group of disorders characterised by high plasma glucose levels [17]. Type 1 diabetes, which represents 5–10% of all diabetes, is caused by autoimmune destruction of β cells leading to usually absolute insulin deficiency. Type 2 diabetes is described below, but not all diabetic patients can be easily classified as type 1 or type 2 diabetics. Type 1 and type 2 diabetes may also share common environmental factors [18, 19]. Diabetes during pregnancy, i.e. gestational diabetes, is a temporary form of diabetes but it increases the risk of later developing type 2 diabetes. Other specific types of diabetes include β cell destruction caused by other diseases, drugs, and chemical agents and other genetic defects in insulin or β cell function [17, 20].

The most common type of diabetes, type 2 diabetes, is caused by progressive β cell failure causing defect insulin secretion most often preceded by insulin resistance. Insulin resistance could be described as a subnormal biological response to a given concentration of insulin. Longitudinal studies of individuals that develop type 2 diabetes showed a rise in insulin levels in the normoglycaemic and prediabetes phases that kept glycaemia near normal despite the insulin resistance, followed by a decline in insulin levels and elevated glucose levels when β cell failure occurred. The biochemical mechanisms leading to the progressive β cell failure are not fully known, but elevated glucose levels in combination with excess free fatty acids (glucolipotoxicity) has been demonstrated to harm β cells [21, 22].

Overnutrition and lack of physical activity in subjects that have underlying genetic and acquired predispositions could lead to both insulin resistance and β cell dysfunction [22]. Indeed, the majority of patients with type 2 diabetes are obese, and obesity itself causes or aggravates insulin resistance [23]. The fat distribution within the body is of importance for the risk of developing type 2 diabetes. Abdominal obesity has been shown to be an independent risk factor for type 2 diabetes and abdominal fat tissue can release free fatty acids and inflammatory cytokines that may play a role in the pathogenesis of insulin resistance and thus type 2 diabetes [22, 24, 25].

Since 1965 the World Health Organization (WHO) has published guidelines for the diagnosis and classification of diabetes. The latest version was published in 2006 and the diagnostic criteria for diabetes established in the 1998 WHO guidelines were maintained: fasting plasma glucose at ≥7.0 mmol/L or 2-hr plasma glucose at ≥11.1 mmol/L after ingestion of a 75 g oral glucose load, i.e. an OGTT. The diagnostic fasting plasma glucose cut-point of 7.0 mmol/L was determined as the level at which the risk of retinopathy increased [26]. However, more recent data from three population-based studies suggest a more gradual increase of retinopathy prevalence with fasting plasma glucose and little evidence of a glycaemic threshold [27]. No definite glucose threshold for mortality or cardiovascular risk has been identified but the WHO concluded that the present diagnostic criteria for diabetes distinguish a group with significantly increased premature mortality and increased risk of microvascular and cardiovascular complications [26].
Clinical features
Classical diabetic symptoms include increased urine output (polyuria) and thirst (polydipsia) due to increased fluid loss by the kidney when the plasma glucose level rises above the kidney threshold and excess glucose is being filtered carried by water. Since diagnosis is based on plasma glucose levels and because it often takes several years for type 2 diabetes to progress as far as the kidney threshold, patients may have no clinical symptoms at all when they are diagnosed with diabetes [28]. On the other hand, patients may have symptoms at the time of diagnosis related to hyperglycaemia, i.e. polyuria, polydipsia, blurred vision or opportunistic fungal or bacterial infections, or even symptoms related to secondary complications such as foot ulcers secondary to neuropathy and cardiovascular disease due to delayed diagnosis [29].

Diabetes complications include acute, life threatening complications such as hyper-, or in the case of medical glucose-lowering treatment, hypoglycaemia. Macrovascular disease, i.e. cardiovascular disease (CVD) and microvascular complications, i.e. nephropathy, retinopathy, and neuropathy are considered long-term diabetes complications. The duration of glycaemic burden is a strong predictor of adverse outcome [22]. Time trends and clinical practice in the treatment of CVD risk factors in patients with type 2 diabetes is the focus of this thesis and thus, however important, microvascular complications will not be explored further.

Opportunistic screening for type 2 diabetes
Delayed diabetes diagnosis, and along with it a greater risk of complications, has been recognised as a clinical problem [30]. From studies of retinopathy it has been concluded that the début of the disease could lie at least 4–7 years prior to clinical diagnosis [31]. By screening high risk individuals, especially patients with type 2 diabetes-related conditions such as hypertension, coronary heart disease, obesity or dyslipidaemia or a family history of diabetes, for diabetes, it may be possible to diagnose them at an earlier stage [20]. There are data that indicate an increased proportion of screening-diagnosed patients with type 2 diabetes in the last decades. In a Danish study of newly diagnosed patients with type 2 diabetes during 1989–1992, 75.7% of the diabetic patients presented with typical symptoms which lead to diagnostic testing while 3.2% were tested because of present hypertension [29]. In a more recent study, 40% of the newly diagnosed patients with type 2 diabetes between 2001 and 2006 were asymptomatic and 36% of these were screened for diabetes because of either ischemic heart disease or hypertension, i.e. opportunistic screening [32]. In a US study of clinical practice from the year 2000, 83% of high-risk individuals were screened for diabetes [33]. Liberal testing in clinical practice for random plasma glucose, especially in high risk individuals, has been described and is also advocated by ADA and various authors [6, 20, 28, 34]. Thus, differences in the prevalence of diabetes complications in studies might result from differences in true, rather than known, diabetes duration between populations.
It is often said that there are as many unknown as known diabetics in the general population [15]. Thus, it can be argued that opportunistic screening would identify unknown diabetics that may or may not resemble patients with known diabetes. The findings of similar prevalence of hypertension, about 60–70%, and dyslipidaemia, about 78%, in opportunistic screening-detected diabetic patients as in clinically newly diagnosed diabetic patients seem to support this suggestion. However, HbA1c was lower in screening-detected, 6.7%, than in clinically diagnosed, 7.5%, diabetic patients which indicates shorter diabetes duration in opportunistic screening-detected diabetic patients [35, 36].

Opportunistic screening aims to detect diabetes at an early stage and thus provide the opportunity for early intervention against CVD. However, it is not known if opportunistic screening reduces the risk of cardiovascular complications.

**Cardiovascular disease in patients with diabetes**

Cardiovascular disease includes diseases that affect the cardiovascular system, i.e. heart and blood vessels. The term can be used to include coronary heart disease (CHD), i.e. ischemic heart disease, myocardial infarction (MI), and angina pectoris, as well as cerebrovascular disease (stroke), heart failure, congenital and rheumatic heart diseases, and peripheral artery disease. Different studies on CVD in diabetes might include all of these or a selection thereof, most often CVD related to atherosclerosis, i.e. CHD or heart failure, cerebrovascular disease, peripheral artery disease, or sudden death assumed to have been caused by CHD (Figure 1).

![Figure 1. Relative risk of CVD in subjects with and without diabetes: Framingham Heart Study. Kannel WB et al. Am Heart J. 1990;120:672-676.](image-url)

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Atherosclerotic CVD has been shown to be more common and severe than microvascular complications in patients with type 2 diabetes [37]. Diabetic patients also suffer more complications and more severe outcomes than patients without diabetes once cardiovascular disease is established. This might result from diabetes-specific changes in the arteries but the mechanisms remain unclear [38].

In this thesis the main focus lies on the prevention of atherosclerotic CVD and in particular CHD.

**Coronary heart disease**

*Incidence*

Coronary heart disease is the leading cause of death in patients with type 2 diabetes [39, 40] and it follows that the focus to date has been on preventing CHD in these patients. In a study from Finland by Haffner et al. it was concluded that CHD mortality in patients with type 2 diabetes without prior MI did not differ from CHD mortality in non-diabetic patients with prior MI after adjustment for CVD risk factors. Consequently, type 2 diabetes could be regarded as a CHD equivalent [41]. This concept has recently been questioned and in a meta-analysis of 13 studies enabling comparison of CHD events in diabetic and non-diabetic patients it was concluded that diabetic patients without prior MI had a significant 43% lower risk for total CHD events (OR 0.56, 95% CI 0.53–0.60) than the non-diabetics with previous MI and that type 2 diabetes cannot be regarded as a CHD equivalent. Eleven of the included studies showed similar results as the meta-analysis, while only one supported the study by Haffner et al., which was also included in the meta-analysis. The authors argued that primary prevention strategy to prevent cardiovascular disease in patients with diabetes should still be based on the patient’s absolute risk of developing cardiovascular events rather than preventive treatment irrespective of the patient’s absolute CHD risk [42].

The incidence of myocardial infarction in diabetic patients does not show the same favourable trend as in the general population. The incidence of MI has declined in the general population and population-based data in Germany from 1985–2006 showed a 27% decline in MI incidence in women with diabetes, similar to that in non-diabetic women, but a 25% increase in MI incidence in men with diabetes; MI incidence in non-diabetic men declined by 34% in the same time period [43]. Northern Sweden MONICA data from 1989–2000 demonstrate a decrease in first MIs in non-diabetic men but not in women. There were no changes in the incidence of first MIs in men or women with known diabetes in the same data [44] (Figure 2).
Figure 2. Incidence of first myocardial infarction (MI) in northern Sweden in patients without (a) and with (b) diabetes, according to gender.

Clinical features of CHD in patients with diabetes

The more severe risk of fatal outcome of CHD in patients with type 2 diabetes is well established. The most common specific mortality causes in diabetic patients after MI are heart failure and fatal re-infarction [45, 46, 47]. Diabetes is an independent marker of post MI mortality and has been estimated to double the risk of a fatal outcome [45, 48, 49]. This level of increased risk was confirmed in a recent meta-analysis of 37 prospective cohort studies in type 2 diabetes that also found that women have a 50% higher relative risk for fatal coronary heart disease than men. The authors concluded that this greater excess coronary risk could be explained by more adverse cardiovascular risk profiles in women with diabetes, combined with possible disparities in treatment that favour men [50].

A sex difference was also shown in a study of 2,634 diabetes patients with MI from the US. During 1975–1999 a decrease in hospital case fatality rates after MI in both men and women was observed, although interestingly the in-hospital death rate was higher in women than in men during the study period [51].

Several factors may contribute to the unfavourable prognosis of CHD in type 2 diabetes; for example, patients with type 2 diabetes suffer from a more severe and diffuse coronary atherosclerosis when diagnosed with CHD [46, 52] than non-diabetics. Diabetes-induced unfavourable alterations in coagulation and increased platelet aggregation and adhesion as well as diabetic cardiomyopathy and disturbed autonomic balance could also contribute to the impaired outcome after MIs [46, 53, 54]. Acute interventions and secondary prevention in the treatment of MI patients may also influence the outcome. Underutilisation of evidence-based treatment in type 2 diabetes during MI-related hospital stays was demonstrated in a study of coronary units in Sweden in 1995–1998; diabetic patients received less intervention and secondary prevention than non-diabetic patients [55]. In a more recent study of 412 US hospitals, the differences in treatment between MI patients with or without diabetes were no longer obvious. Patients with type 2 diabetes received acute medication and intervention as well as secondary prevention with ASA, β-blockers, statins, cardiac rehabilitation, and smoking cessation counselling to the same extent as non-diabetic patients after MIs. However, treatment differed between insulin-treated diabetic patients and non-diabetic patients. Also worth noting is that the risk of in-hospital death was increased in patients with type 2 diabetes compared to non-diabetic patients [56].

Silent myocardial ischemia and silent MIs, i.e. without chest pain or other symptoms, are interesting as they could allow CHD to progress undetected and thus help worsen the prognosis. In the Framingham Heart Study it was concluded from biennial ECGs that ‘silent’ MIs, presented as incident Q waves, were as likely to cause death, heart failure, and stroke as recognised MIs in a general population [57]. Both silent myocardial ischemia and silent MI were more common among diabetic patients than non-diabetics and it has been argued that autonomic neuropathy is the explanation for these findings [58, 59].
INTRODUCTION

Silent MI was most common among patients with known ischemic heart disease and, in spite of diagnostic difficulties, the prevalence in asymptomatic diabetic patients was described as significant [59, 60]. The generally more advanced CHD in patients with type 2 diabetes was demonstrated in a study aiming to evaluate ADA guidelines. Severe coronary atherosclerosis was demonstrated in about 65% of the patients without history or symptoms of CHD regardless of number of CHD risk factors [61].

Screening for CHD in patients with diabetes

Knowledge of the high prevalence of coronary atherosclerosis even in asymptomatic patients with type 2 diabetes has lead to the testing of the use of screening for CHD. In the DIAD study, a randomised controlled trial that included patients with type 2 diabetes (mean age 60.7 years, mean diabetes duration 8.2 years, and without symptoms or signs indicating CHD), 22% had silent ischemia when performing adenosine-stress single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) [62]. Three years after the initial examination, 79% of the patients with abnormal findings demonstrated resolution of the findings, potentially because of intensified aggressive medical treatment of CVD risk factors. However, there are no RCT data to support this conclusion [63]. The cardiac event rate (2.9% suffered MI or cardiac death) was also much lower in the DIAD study than expected after 4.8 years. No influence of CHD screening on events was detected, but the low event rate could cause a lack of power to demonstrate possible differences. It was argued that significantly increased lipid-lowering, antihypertensive, glucose-lowering, and ASA treatment between screening and follow-up could contribute to the low incidence of MI and cardiac death [64].

Mortality and time trends in mortality

Recent studies on time trends in CHD and CVD mortality in people with type 2 diabetes have shown diverging results. Both a decline in CVD mortality and unchanged outcome has been demonstrated in studies from Western countries since the 1980s. In two large Norwegian population-based cohorts from the 1980s and the 1990s that were both followed for nine years, lowered CHD mortality in people with type 2 diabetes was demonstrated, similar to the trend in the general population. In the age group 70–79 years old, mortality per 1,000 person-years in men declined by 54% and in women by 59% among patients with type 2 diabetes [65]. Improved age-adjusted 10-year observed survival rate in diabetic patients from 1980-1984 to 1995–1999 was also demonstrated in cross-sectional population-based data from Sweden. Survival increased in men with diabetes from 41.4% to 51.5% and in women from 43.7% to 61.0% between the two time periods [66]. The general argument was that improved primary CVD prevention in diabetic patients could cause the improved survival. There were no differences between the sexes in these Scandinavian studies. However,
improved survival in male, but not female, patients with type 2 diabetes was reported in NHANES data from the US between 1971 and 1986 and between 1988 and 2000. The authors suggest that less aggressive medical treatment in women as well as differences in pathophysiology between men and women are probable causes of the lack of improvement among women [67]. In contradiction to these favourable trends, the Northern Sweden MONICA Project revealed no improvement during 1989–2000 in case-fatalities in men or women with known diabetes who suffered an MI. In non-diabetic participants, both the incidence of, and case-fatality in MI decreased during the same time period resulting in reduced CHD mortality in the general population [44].

Regardless of the time trends in CHD mortality, diabetic patients still suffer from a significantly enhanced risk of dying from CHD compared to people without diabetes. Mortality from CHD was about twofold in male and female diabetic patients compared to people without diabetes in both the Norwegian study (adjusted for age, hypertension, body mass index, smoking, exercise, and education) and the Swedish study (adjusted for age, daily smoking, socioeconomic status, CHD, and hypertension) [65, 66]. Also in NHANES in 1988–2000, both age-adjusted CVD and total mortality rates were more than twofold in both men and women with diabetes compared to people without diabetes [67]. Diverging results were demonstrated in a Dutch prospective cohort study comprising 973 patients with type 2 diabetes, mean age 66 years, followed for 5.4 years in 2001–2007. Life expectancy for the diabetic patients in the study was similar to the general population, except for patients with a history of cardiovascular disease, HR 1.71, 95% CI 1.23–2.73, or albuminuria, HR 2.59, 95% CI 1.56–4.28. Diabetes duration, smoking, or systolic blood pressure did not influence all-cause or CVD mortality. It should be noted that the patients’ diabetes duration was rather short with a mean of 4.2 years, and that they participated in a shared care project where the patients were treated by their GPs, supported by diabetes specialist nurses, and advised by internists. However, the authors argued that the participants could be representative of patients with type 2 diabetes in other countries with structured care as well [68].

**Risk factors and their associations with cardiovascular disease**

The Framingham Heart Study, from which results began to be published in 1957, was one of the earliest to use the term “risk factor” for etiological factors that increase the risk of cardiovascular disease [69]. Smoking, high blood pressure, high blood cholesterol, and overweight were identified risk factors for CVD in the Framingham Heart Study. The investigators found that multiple risk factors in the same person increased risk a lot above the sum of the individual risk factors. Another important finding was that CVD mortality was about the same in men as in women with diabetes. The Framingham Heart Study also identified diabetes as an independent risk factor for CVD, which has been confirmed in later studies [70, 71].
The fact that people with diabetes suffer increased risk of CVD has inspired prospective cohort studies in order to identify the influence of potential risk factors also in diabetic patients. It has further been confirmed that smoking, high blood pressure, and dyslipidaemia are risk factors for CVD in diabetic patients [72, 73]. In addition, fasting plasma glucose, proteinuria, the presence of retinopathy, and BMI were found to independently influence CVD risk and CVD mortality in diabetic patients [74, 75, 76]. Patients with type 2 diabetes also have CVD risk factors such as hypertension and hyperlipidaemia to a greater extent than patients without diabetes [38, 77]

Blood glucose

Several studies have investigated the association between blood glucose and CVD risk and a relationship between both fasting and 2-hr post-challenge glucose and fatal and non-fatal CVD has been confirmed [78, 79, 80, 81, 82]. Most of these studies have established a continuous relationship between plasma glucose and cardiovascular disease from levels below the diabetes diagnosis threshold, although some identified a threshold effect. In vitro, animal, and also human studies have suggested several ways in which glucose can be harmful to the arterial wall and cause atherosclerosis and thus cardiovascular disease. Hyperglycaemia has been shown to stimulate the adhesion of monocytes to the endothelium and lipid-stimulated proliferation into macrophages and also smooth muscle cell proliferation and migration into the intima where also glucose-stimulated oxidative stress and inflammation could contribute to the atherosclerotic process [83] (Figure 3). Still, it was only in a recent meta-analysis of five large randomised controlled trials (the UKPDS, PROactive, ADVANCE, VADT, and ACCORD studies) that reduced CHD incidence by 15–17% with better glucose control in patients with type 2 diabetes was demonstrated. The mean HbA1c concentration was 0.9%, 95% CI 0.88–0.92, lower in the intensively treated group than in patients receiving standard treatment. The overall mean HbA1c was 6.6 (± 0.8)% in the intensively treated group and 7.5 (± 1.1)% in the group receiving standard treatment. The individual trials did not report significant reduction of primary end-points. No effect of glucose lowering on all-cause mortality was found in the meta-analysis [84]. In two of the studies, namely ACCORD and VADT, mortality increased in the intensively treated groups, which has been interpreted as increased vulnerability to hypoglycaemia in patients with long-standing, ≥10 years, diabetes [85, 86]. In the UKPDS study, the differences in HbA1c concentration between groups during the study period were lost at the end of the trial. A 10 year post-trial extension, however, showed reduction in MI by 15–33% and all-cause mortality by 13–27% in groups with better glucose control during the study period. The authors advocated optimal glycaemic control already from the time of diabetes diagnosis in order to prevent CVD and other complications [87].
Blood pressure

Elevated blood pressure is an established risk factor for cardiovascular disease pursuing its harmful effect on the endothelium in the arteries worsening the atherosclerotic process. The risk of cardiovascular diseases increases continuously as blood pressure rises from levels that are considered to be within the normal range [88]. The majority of patients with type 2 diabetes are also hypertensive which enhances the risk of CVD [89]. The beneficial effect of blood pressure lowering has been demonstrated in four major RCT studies. The increased impact of hypertension on CVD risk in type 2 diabetes was shown in one of the first placebo-controlled studies comparing effect of blood pressure lowering in diabetic and non-diabetic patients, the SHEP study. The treatment target was lowered blood pressure by 20 mm, and during the trial mean blood pressure lowering in diabetic patients was 9.8/2.2 mmHg and in non-diabetic patients 12.5/4.1 mmHg. Anti-hypertensive treatment prevented 101/1,000 diabetic patients and 51/1,000 non-diabetic patients from having a major CVD event after five years [90]. The cardioprotective effect of intensive treatment of elevated blood pressure in diabetic patients was also demonstrated in the UKPDS. The study comprised newly diagnosed hypertensive type 2 diabetes patients. After nine years, patients assigned to intensive treatment of blood
pressure had reduced risk of diabetes-related outcomes (sudden death, death from hyperglycaemia or hypoglycaemia, fatal or nonfatal MI, angina, heart failure, stroke, renal failure, amputation, vitreous haemorrhage, retinal photocoagulation, blindness in one eye, and cataract extraction) and death related to diabetes but not all-cause mortality. The number needed to treat to prevent one diabetes-related outcome was 6.1, 95% CI 2.6–9.5, and to prevent death from a diabetes-related cause 15.0, 95% CI 12.1–17.0. Mean blood pressure after nine years of follow-up was 144/82 in patients assigned to intensive treatment, while mean blood pressure in patients assigned to less intensive treatment was 154/87. It should be noted that the majority of the patients in the tight blood pressure group required two or more antihypertensive drugs, and 29% required three or more drugs [91]. In the HOT study, where the aim was to evaluate optimal target blood pressure, diabetic patients in the target group of diastolic blood pressure ≤ 80 mmHg reduced major CVD events by 51% compared with patients in the target group ≤ 90 mmHg. Mean baseline diastolic blood pressure was 105.4 mmHg in all patients in the study and achieved mean diastolic blood pressure was 81.1 mmHg in the ≤ 80 mmHg target group and 85.2 mmHg in the ≤ 90 mmHg target group. The systolic blood pressure was reduced by 26.2 mmHg in the ≤ 80 mmHg target group and by 29.9 mmHg in the ≤ 90 mmHg target group [92]. Diabetic patients with earlier CVD events or at least one CVD risk factor who participated in the HOPE study decreased their risk of MI and stroke more than what was to be expected from the observed blood pressure lowering, and the protective effect of ACE inhibitors on the arterial wall was considered a possible explanation [93, 94]. The benefits of blood pressure lowering on CVD end points usually appear within months [95, 96]. In a post-trial follow-up of the UKPDS, no sustained effect of the benefits of initial blood pressure lowering was seen. Since between-group differences in blood pressure were lost within two years after the trial, it was concluded that good blood pressure control must be continued if benefits are to be maintained [97].

Blood lipids

Diabetic dyslipidaemia is strongly related to atherosclerosis. Defect genesis and handling of fatty acids along with an increased number of small dense LDL-particles, typical for diabetic dyslipidaemia, are considered factors that increase atherosclerosis. In addition, the reversal of atherosclerosis through the removal of cholesterol from atherosclerotic plaque cells in the arterial wall is supposed to be impaired in diabetic patients due to lower HDL levels in general [83] (Figure 4). Effects of lipid-lowering treatment in patients with diabetes were studied in a meta-analysis of 14 randomised trials of statins, published in 2005. The investigators found that there is an almost linear relationship between the absolute risk reductions in LDL cholesterol and the proportional reductions of CHD and other major CVD events. The risk reductions were largely independent of pre-treatment lipid levels. No differences in risk reduction between type 2
diabetic and non-diabetic patients were observed. In all diabetic patients, statin therapy reduced the 5-year incidence of major vascular events by about 20% per mmol/L reduction in LDL cholesterol. Thus it was concluded that standard doses of statins, estimated to lower LDL by 1.5 mmol/L, would reduce major vascular events by approximately 30% [98]. Pharmacological intervention, but not target achievement, against hypercholesterolemia was also evaluated in another meta-analysis. It was concluded that most type 2 diabetic patients benefit from statin therapy regardless of initial lipid levels. The number needed to treat to avoid one CVD event was 33–34 for primary and 13–14 for secondary prevention [99]. The benefits of lipid lowering on CVD outcome seem to appear after 1–2 years [100, 101, 102].

Figure 4. Diabetic dyslipidemia and the vessel wall.

Other risk factors
There are no RCTs that evaluate the effect of weight change on CVD. Observational studies have shown conflicting results concerning the association between BMI and CVD in patients with type 2 diabetes [103, 104, 105, 106]. Recently, a large cohort-study from the NDR showed adjusted hazard ratios of CHD, CVD, and total mortality with 5 units increase in BMI of 1.09, 95% CI 1.03–1.16, 1.07, 95% CI 1.02–1.12, and 1.20, 95% CI 1.20–1.30, respectively [76]. BMI is closely related to other CVD risk factors such as hypertension, hyperglycaemia, hyperli-
pidaemia, and microalbuminuria. This has lead the WHO to suggest that, in risk evaluation of BMI, these risk factors should not be considered as confounders and adjustments should not be made in order not to underestimate the risk associated with BMI [107]. Observational studies, however, indicate that the adverse effect of BMI on other CVD risk factors could account for 40–55% of the increased risk for CHD and CVD, while other variables related to BMI (e.g. disturbed fibrinolysis, endothelial dysfunction, and low-grade inflammation) also may contribute to the increased CHD risk [76, 108, 109].

The relationship between proteinuria and cardiovascular risk in the general population was established early on in the Framingham Heart Study [110]. In addition to the association with impaired kidney function, excess kidney leakage of protein, proteinuria or microalbuminuria is also an independent risk factor for CVD in patients with type 2 diabetes [74, 75]. Albuminuria was the strongest predictor of CVD outcome in patients with type 2 diabetes and with nephropathy in an RCT study on the effects of drug treatment, and albuminuria reduction was also associated with improved CVD outcome [111]. In an observational study, comprising patients with type 2 diabetes and with microalbuminuria, the risk of CVD events was reduced in patients who achieved a 50% reduction of microalbuminuria during eight years of follow-up [112].

Cigarette smoking was shown to be a significant risk factor for death by coronary heart disease in type 2 diabetes in three large prospective studies, namely the Multiple Risk Factor Intervention Trial (MRFIT), the Finnish Prospective Study, and the Paris Prospective Study [113]. In a statement from ADA, it was later concluded that there are consistent results from both cross-sectional and prospective studies that smoking enhances the risk for micro- and macrovascular disease as well as premature mortality in patients with type 2 diabetes [114]. This was confirmed in a prospective study from the Swedish National Diabetes Register showing increased risk for fatal and non-fatal first MI, stroke, and total mortality in patients with type 2 diabetes who smoked [115]. The benefits of smoking cessation was demonstrated in the Nurses’ Health Study where female patients with type 2 diabetes who currently smoked had an adjusted risk ratio of 7.7 for CHD compared to non-smokers, while CHD risk among those who had stopped smoking 10 years previously was similar to those who had never smoked [116]. The conclusion is that smoking cessation remains the most cost-effective method when it comes to prolonging the life of smoking patients [117].

**Multifactorial intervention**

Results from the Steno-2 study suggest that multifactorial intervention could be more effective than conventional risk factor treatment. Patients with type 2 diabetes and with persistent microalbuminurina were randomly assigned to either intensified, target-driven therapy in line with the latest ADA guidelines or usual care. Dietary changes, increased physical activity, smoking cessation
along with drug treatment targeted the intensively treated group. At the end of follow-up after 13.3 years, the hazard ratios of CVD and all-cause mortality in the intensively treated group were 0.41, 95% CI 0.25–0.67 and 0.54, 95% CI 0.32–0.89, respectively, as compared with the usual care group of patients. Furthermore, early intervention, as compared with late intervention, seemed to increase the beneficial effects of multifactorial intervention on diabetes-related complications and deaths [118].

It should be noted that secondary complications of type 2 diabetes not only include cardiovascular disease, but also microvascular disease such as retinopathy, nephropathy, and neuropathy. Risk factors for CVD such as glycaemia and elevated blood pressure also increase the risk of microvascular complications, and multifactorial intervention against CVD risk factors has been shown to be beneficial in reducing retinopathy, nephropathy, and neuropathy in patients with type 2 diabetes [119]. Single CVD risk factor treatment has also been shown to reduce microvascular complications [91, 93, 120, 121]. Reducing CVD risk will thus also contribute to a reduction of microvascular disease.

Predicting risk for cardiovascular and coronary heart disease

Following the revealed associations between risk factors and CVD, different algorithms have been developed in order to calculate CVD or CHD risk in individuals without overt CVD or CHD. Data from population studies have enabled the prediction of CVD or CHD during follow-up periods spanning several years. Algorithms including variables that were identified as risk factors in the original studies have been created, though authors may have excluded variables if interaction was suspected. The modelling and evaluation of the statistics have then resulted in risk predictive algorithms that are expressed as score sheets or computer-based risk engines. Commonly, these algorithms calculate absolute 10-year risk of CHD, i.e. angina pectoris, MI, and coronary death, and thresholds for primary prevention may be included [122, 123, 124]. The Framingham Heart Study alone has resulted in several risk prediction estimates for CVD outcome and many more risk calculators are now available [125].

The use of CHD risk estimates in patients with type 2 diabetes is not generally recommended in clinical guidelines. However, studies have evaluated the predictive abilities of risk engines also in patients with type 2 diabetes [126, 127, 128, 129, 130]. Both the Framingham risk score and the UKPDS risk engine were moderately effective at identifying those at high risk (discrimination) but underestimated the absolute CHD risk [127, 128, 129]. In the 2008 update on the British National Institute for Clinical Excellence (NICE) clinical guidelines on type 2 diabetes, the Framingham risk score, the UKPDS risk engine, the PROCAM score system, the SCORE risk charts, the DECODE risk score, and the Archimedes model were evaluated. It was concluded that the UKPDS risk engine showed some evidence of validity and could be used for risk evaluation in low risk type 2 diabetic patients and for educational purposes when discuss-
ing CVD complications with an individual [131]. Since then a simplified risk equation based on Swedish NDR data has been published but not yet evaluated in other populations [132]. Another statistical tool designed to predict 6-year CHD mortality in diabetic patients has been criticised for giving anomalous results [133, 134]. Griffin et al. recently evaluated the Framingham risk score and the UKPDS risk engine in the EPIC-Norfolk cohort, an observational prospective study. The results indicated similar discrimination between the two risk calculations, but in this study both were found to overestimate risk also in diabetic patients [135].

**Guidelines for CVD prevention in type 2 diabetes**

Clinical practice guidelines (CPGs) for the treatment of type 2 diabetes have been developed in several countries and include measures to prevent CVD [20, 39, 88, 131, 136, 137,]. In this thesis, the treatment of CVD risk factors in the Swedish national guidelines from 1999 was evaluated (Figure 5). However, European guidelines, published in 2003, were cited in the treatment recommendations of the Swedish Medical Products Agency in 2006 and these may also have influenced diabetes care in Sweden [88, 138]. New Swedish national guidelines for the treatment of diabetes are expected to be published in 2010.

- Quality of care – participation in national registry for diabetic patients
- Individual agreement with the patient – information, responsibility, treatment goals, consent
- Diabetes – epidemiology, classification and diagnosis (WHO criteria 1998)
- Screening – risk groups
- Care – role of diabetes nurse, visit intervals and check list
- Treatment – life style changes, coping, guidelines for diet, physical activity, smoking, alcohol.
- Medical treatment – insulin, oral drugs, combinations of these
- Acute complications – hypoglycemia, ketoacidosis, hyperglycemic hyperosmolar syndrome
- Hypertension – drug treatment if BP>140/85, lower if microalbuminuria
- Dyslipidemia – life style changes 3-6 months and then drug treatment if P-total cholesterol>5 mmol/l or P-LDL>3 mmol/l, CVD risk equal to patients with established CVD.
- Pregnancy – treatment and care, gestational diabetes, contraceptives
- Late complications – screening and diagnostic tests for nefropathy, neuropathy, sexual problems, foot problems, peripheral artery disease, coronary heart disease, cerebrovascular disease, musculoskeletal system problems, dental problems.

**Figure 5.** Contents of the Swedish National Guidelines for the Care and Treatment of Diabetes Mellitus 1999.
In a preliminary release from the new national guidelines for the treatment of diabetes from the Swedish Board of Health it was underlined that treatment goals are based on consensus and results from only a few observational and RCT studies. It was considered particularly important that the concentration on treatment goal achievement should not be too high in the evaluation of benefit against risk. Future studies on the treatment goals for HbA1c, LDL cholesterol, and blood pressure, as well as new treatment alternatives, might result in reassessment of treatment goals [139]. This communication was preceded by a reappraisal of the European guidelines on hypertension stating that the evidence of a blood pressure target below 130/80 in diabetes patients is almost non-existing and that antihypertensive treatment should start when blood pressure is above 140/90 aiming “to pursue a sizeable blood pressure reduction”. In patients with high cardiovascular risk, the lowering of blood pressure close to or below 120–125/70–75 should not be pursued due to a J-curve phenomenon in the relation between blood pressure and CHD incidence. Glucose targets were not changed but, referring to the ACCORD study, it was stated that tight glucose control should be pursued gently and that HbA1c levels below 6.5% should be avoided [140]. Based on the long-term follow-up data from the UKPDS and DCCT studies a treatment goal of HbA1c < 7% has been proposed for most patients. In patients with long-standing diabetes, a history of severe hypoglycaemia, limited life expectancy, advanced microvascular or macrovascular complications, or extensive comorbid conditions, less stringent HbA1c goals were proposed [20].

The use of risk stratification in clinical decision-making has been promoted in some guidelines [131, 141]. As the relative CVD risk reduction is constant in statin therapy, patients with the highest absolute CHD risk will benefit most from intervention. In Britain, the National Institute for Clinical Excellence (NICE) therefore recommended primary prevention with statins for patients with type 2 diabetes with a calculated absolute 10-year CHD risk of > 15%. However, it was suggested that cardiovascular risk estimation should only be used once a year in diabetic patients over the age of 40 who were of normal weight, normotensive, did not have microalbuminuria, were non-smokers, did not have a high-risk lipid profile, and had no history of CVD in their own or family background. All other patients with type 2 diabetes should be considered to be at high, ≥ 20%, CVD risk, particularly as MI outcome is known to be worse in patients with type 2 diabetes and preventive therapy therefore is more cost-effective [131]. Sweden, as other countries, have adopted lipid thresholds and targets for secondary prevention in CHD patients in order to identify patients with type 2 diabetes who should receive lipid-lowering therapy [20, 136, 142].

Smoking cessation was generally recommended in the guidelines [20, 131, 136].
Guideline adherence

Authors who have identified improvements in different aspects of CHD outcome in patients with type 2 diabetes in observational studies have suggested that improved CVD prevention during recent years could explain their results [64, 65, 67]. Numerous studies from different countries, however, have revealed discrepancies between guidelines and treatment practice in diabetes care, especially in the prevention of CVD. Treatment goals for blood pressure and lipids were achieved in less than or about half of patients with type 2 diabetes in observational studies [143, 144, 145, 146, 147, 148, 149, 150, 151]. In patients with type 2 diabetes and with CHD in the Swedish NDR, risk factor levels were lower in 2005 than in an earlier study from 1999–2000, but 40% of the CHD patients did not achieve treatment goals for lipids in 2005 [152].

There were also wide variations in standards of care processes, resources, and patients’ knowledge of diabetes in a British audit of diabetes care [153]. Divergence between physicians’ beliefs and treatment practices has also been demonstrated previously [154].

Patients’ beliefs and understanding of diabetes and cardiovascular risk can also influence guideline implementation and the prevention of CVD. In a British study, type 2 patients who were interviewed were unaware of how strongly diabetes influences cardiovascular risk. The patients were more likely to attribute CVD to external or unchangeable factors like “stress” and “heredity”, than medical risk factors like cholesterol and smoking [155]. Mismatch between physicians and patients with type 2 diabetes risk perceptions was also shown in a Dutch cross-sectional study. Following a consultation where CVD risk was discussed nearly four in five high-risk patients incorrectly estimated their risk as lower than the actual risk, while one in five low-risk patients was unjustifiably pessimistic about the risk of CVD [156]. Based on this study, increased awareness among physicians about diabetic patients’ beliefs and understanding of CVD risk and improved communication skills is called for.

It has been argued that the current treatment targets in type 2 diabetes for glycaemia, blood pressure, and lipids are only achieved in 50–70% of patients, including in research studies, and that individually tailored targets are needed [157]. The both favourable and limiting effect of guidelines on clinical care and the need to tailor treatment practice to the individual patient’s opinion, status, concomitant diseases, and medication has also been expressed by family physicians [158, 159].
RATIONALE FOR THE THESIS

Over the last decades, the overall view of diabetic patients as high-risk individuals for CVD has increased and the importance of lowering risk factor levels has been pointed out as outlined in the previous chapters. Clinical practice guidelines including treatment goals for CVD risk factors in type 2 diabetes have been introduced in Sweden as in other countries as described earlier. Still, in spite of a secular trend of lowered CHD mortality in the general population, CHD mortality has not declined among people with diabetes in Sweden [44]. The impact of the Swedish national guidelines in clinical practice and the effect on CVD prevention among people with type 2 diabetes has not been studied extensively.

In Sweden, patients with type 2 diabetes are typically cared for by general practitioners (GPs) and diabetes nurses at group practices. The ability to identify problems concerning diabetes care, especially relating to CVD prevention, in primary health care could help to improve the outcome of type 2 diabetes. To the best of our knowledge there are no studies on the experiences of diabetes care of Swedish GPs. GPs are responsible for the medical care of diabetic patients, and with the help of their experiences future improvements could be made. Previous studies from other countries that include physicians’ perspectives on diabetes care do not specifically focus CVD prevention [159, 160].
OBJECTIVES

The overall aim of the thesis was to investigate how the treatment goals for CVD risk factors contained in the national guidelines for diabetes care were reflected in clinical practice, and to explore factors that might influence the remaining high incidence of CHD in the type 2 diabetes population.

The specific aims of each paper were:

I. to study whether the introduction of treatment goals for dyslipidaemia was reflected in lower cholesterol levels in patients with diabetes in a general population

II. to explore GP’s experiences regarding treatment practice in type 2 diabetes with specific focus on the prevention of cardiovascular disease

III. to assess whether CHD screening was performed to the same extent as screening for microvascular complications in patients with newly diagnosed type 2 diabetes. In addition, we evaluated whether prevention against CHD had been undertaken when CHD risk was detected

IV. to study time trends and treatment goal achievement in glycaemia, blood pressure, and plasma lipids early in the course of type 2 diabetes and their effect on absolute and modifiable 10-year CHD risk
RESEARCH DESIGN AND METHODS

Study populations

This thesis was based on three study populations. The first was derived from a population-based health survey, the VIP, the second was derived from a national register of diabetes patients, the NDR, and the third consisted of invited family physicians who agreed to participate in focus group interviews.

The Västerbotten intervention program (VIP)

The VIP was initiated in 1985. It is an ongoing health intervention programme in the county of Västerbotten in Sweden which has a total population of 260,000. Up until December 2008, 89,680 unique individuals had participated in the VIP, and of those 30,283 had attended two sessions ten years apart. This program combines a population and an individually orientated strategy with the aim of preventing diabetes and cardiovascular disease.

Both men and women were invited to take part in a health survey at their primary health care centre the year they turned 30, 40, 50, and 60 years of age (since 1996, at 40, 50, and 60 years of age) [161]. The participants underwent a health examination focusing on risk factors for cardiovascular disease and diabetes and answered a comprehensive questionnaire. Height and weight were measured in light indoor clothing without shoes. Body mass index (BMI) was calculated as weight (kg) divided by squared height (m²). Blood pressure was measured after five minutes’ rest in a supine position. Plasma glucose, plasma total cholesterol and plasma triglycerides were analyzed after overnight fast with a dry chemical method (Reflotron®, Boehringer Mannheim, Germany). An oral glucose tolerance test (OGTT) was performed after fasting overnight. Presence of diabetes diagnosis, prior hospital care for MI, use of lipid-lowering agents in the fourteen days before the survey, perceived health, smoking, and exercise habits were reported in a questionnaire. Perceived health, i.e. self-reported subjective health, was measured using the question: “How do you consider your own health in general?” Answers were categorised as “good” (perceived good health), “fair” or “bad” (perceived ill-health). Smokers were defined as those reporting daily smoking. Those who reported that they were ex-smokers or “occasional smokers” were classified as non-smokers. Exercise habits were evaluated using two different parameters: “Walking twice a week or more” and “Regular exercise with the aim of improving physical fitness and/or achieving good health more than once weekly”. The questionnaire also covered other issues but these are not described here since they were not used in the analyses in this thesis.

Each health screening concluded with health counselling. The mean participation rate was 57% during 1990–96, but increased significantly from 1997 onwards, reaching a mean of 65% during the period up to 2008.
Eighty-five percent of participants with either known or screening-detected diabetes in the VIP consented to being included in the DIabetes register of the Västerbotten intervention programmE (DIVE) during 2001–2005.

The Swedish National Diabetes Register (NDR)

The Swedish NDR was initiated in 1996 in response to the demands of the St Vincent declaration for quality assurance in diabetes care [162]. Participation in the NDR is not mandatory, but one aim of the NDR is that ideally all diabetic patients in Sweden should be reported yearly, based on registered annual data from actual patient visits in primary health care or at hospital outpatient clinics. Reported data include demographic data, diabetes duration, treatment modalities, as well as various risk factors and diabetes complications.

In 2008, 219,227 diabetes patients, 79.4% in primary health care, were included in the NDR. In all, about 60% of the estimated number of diabetic patients in Sweden was reported in the NDR. There were geographical differences in reporting frequency and the estimated participation rate in the NDR in primary health care in different counties varied between 24.7% and 72.6% in 2008 [163].

After statistical analysis, all participating centres have received an annual report containing local results as well as comparisons between national data. The NDR is probably among the largest national diabetes registers in the world. Further, it is thought that the unique size of the NDR, with repeated annual surveys and with a geographical distribution all over Sweden, results in a reasonably accurate reflection of treatment traditions and results in Sweden as a whole.

Methods

Paper I

Study participants

This was a retrospective explorative descriptive cross-sectional study of altogether 59,338 subjects from ten consecutive VIP cross-sections, in 1995–2004. Data from the VIP health examination and questionnaire were used in the analyses.

Participants with known diabetes were identified using the questionnaire.

Design

In order to evaluate whether the introduction of the national guidelines for the treatment of type 2 diabetes had had any impact on cholesterol levels, results were presented in two periods, Period I (1995–1999) and Period II (2000–2004), i.e. before and after the Swedish national guidelines were introduced in 1999 [136].

Cholesterol levels in participants with known diabetes were compared to those of non-diabetic survey participants of the same age and sex in order to
compare with any time trend in the general population. The influence of BMI, use of lipid-lowering drugs, physical exercise, and smoking on cholesterol levels was evaluated.

**Paper II**

*Design*

Focus group method was used. We developed an interview guideline in order to cover the topic and stimulate discussion (Table 1). Further detailed discussions were stimulated using open-ended questions like “Could you please elaborate on what you mean?”

**Table 1.** Thematic guide for focus group interviews.

- What is a good management of diabetic patients?
- What do you regard as most important in the encounter with diabetic patients?
- What does prevention in diabetes care mean in your opinion? What are the most important goals in the prevention in diabetic patients? What is most important to achieve?
- Who is responsible for preventive measures in your opinion? That is, how is responsibility distributed?
- What is necessary to succeed in preventing cardiovascular disease (CVD) in patients with typ 2 diabetes?
- What is your opinion on guidelines (national, local) for the prevention of CVD in clinical practice? How can they be used?
- What obstacles do you think exist in the realization of guidelines?
- In the best of worlds – what do you think is required to achieve better prevention of CVD?
- What would help to improve your work with diabetic patients?
- What would improve the patients’ situation?
- How do you know that you do a good job? What kind of feedback do you receive? What means of follow-up are there, for individual patients and for the whole group of diabetic patients?

**Study participants**

In order to identify suitable informants, we contacted health care centre managers in the County of Västerbotten, Sweden, and asked for names of experienced GPs, both men and women, who cared for patients with type 2 diabetes within their practices. All in all, 42 GPs were invited to take part in the study. Fourteen GPs from nine different group practices chose to participate. Two GPs in one of the focus groups worked at the same practice, the others knew of each other but did not work together. The GPs that chose not to participate were not asked why, but a majority spontaneously mentioned other engagements, meetings, or leave of absence and two GPs explicitly declared that they did not want to be interviewed. One GP agreed to participate in the study, but did not show
The four focus groups consisted of 3 (M/F;1/2); 3 (M/F;3/0); 3 (M/F;1/2), and 5 (M/F;1/4) participants respectively (Table 2). Interviews were conducted between January and May 2007.

Table 2. Characteristics of family physicians participating in the focus group interviews.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>6/8</td>
</tr>
<tr>
<td>Age (median, range)</td>
<td>54 (43–64)</td>
</tr>
<tr>
<td>Years since medical degree (median, range)</td>
<td>24 (10–36)</td>
</tr>
<tr>
<td>Rural/Urban practice (n)</td>
<td>5/9</td>
</tr>
<tr>
<td>Appointed diabetes responsibility (n)</td>
<td>5</td>
</tr>
</tbody>
</table>

**Interview method and analysis**

The moderator, a registered nurse who has moderated several focus groups, introduced and led the discussions while the first author (EF) observed, took field notes, and handled the technical equipment. The moderator encouraged all GPs to participate in the discussion and ensured that the questions from the interview guidelines were covered. The interviews lasted about one and a half hours and were recorded digitally and transcribed verbatim.

The transcribed interviews were analysed according to qualitative content analysis [164]. Following the first interview, it was decided that the interview guidelines served their purpose. When the interviews were completed, each of the authors (EF, OR, EEJ) read the texts and “units of meaning” were identified. The process of analysis included both naive reading of the transcribed interviews to obtain a sense of the whole and interpretation of the latent content of the interviews. In a number of meetings between the authors, the findings that had emerged from the interviews were discussed and the units of meanings were coded and grouped into categories and themes. An example of coding and categorisation is shown in Table 3. After the fourth interview, analysis revealed no new categories and it was decided that saturation was fulfilled.
Table 3. Example of Meaning Units, Codes, Categories and Theme.

<table>
<thead>
<tr>
<th>Meaning Units</th>
<th>Codes</th>
<th>Category</th>
<th>Theme</th>
</tr>
</thead>
<tbody>
<tr>
<td>“to prevent the development of stroke and myocardial infarction”</td>
<td>Treatment goals</td>
<td>To integrate science into reality</td>
<td>Dilemma</td>
</tr>
<tr>
<td>“good lipid values and lowered A1C and a good blood pressure and reduced risk factors”</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“the individual is naturally the basis”</td>
<td>Questioning guidelines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“and I don’t recognize the patient”</td>
<td>Supporting guidelines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“it’s more surprising that guidelines are so poorly followed”</td>
<td>Diagnosis without symptoms</td>
<td>To label someone that feels healthy as ill</td>
<td></td>
</tr>
<tr>
<td>&quot;pretty dramatic for someone who doesn’t regard himself as ill”</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“sometimes it’s like burden them with diabetes, a disease, and then they become weighed down”</td>
<td>Making the patient feel bad</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Paper III

Design and study participants

This was a retrospective explorative cross-sectional study of 201 (M/F 122/79, mean age 55.9±6.5 years) screening-diagnosed patients with type 2 diabetes in the DIVE from 1 January 2001 to 30 June 2005. Patients were diagnosed by fasting plasma glucose or an OGTT when participating in the VIP at 34 primary health care centres. The clinical diabetes diagnosis was then verified and classified according to the WHO criteria [17].

Assessment of screening and CHD prevention

We scrutinised the computerised medical records 1.5±0.7 years after diagnosis of diabetes. We further expected that screening for diabetes complications had been undertaken during this time span and that primary or secondary preventive measures had been taken. A diagnosis of CHD (MI, angina pectoris, percutaneous coronary intervention, and/or coronary artery bypass graft) was also noted, as were prescriptions of lipid-lowering medication and acetyl salicylic acid (ASA).

The recommended examinations in screening for microvascular disease in the Swedish national guidelines included a urine sample for detection of microalbuminuria, referral to retinal photography for detection of retinopathy, and screening for peripheral neuropathy by use of a tuning fork and monofilament [136]. Three methods for albuminuria screening were used: urine dipstick testing, 24-h urinary collection, and measurement of albumin creatinine ratio (ACR). Signs of retinopathy, nephropathy, and neuropathy were defined as microvascular complications.
In addition, the national guidelines recommended that an ECG for the detection of CHD [136] was performed at the time of diagnosis of diabetes. ECGs were digitally filed in the patients’ medical charts. In order to evaluate whether there was a difference between screening for microvascular complications and CHD, the proportion of patients who had an ECG registered was compared to the proportion of patients who were screened for each of the microvascular complications.

The use of a cardiovascular risk score was also noted as an indicator of awareness of cardiovascular disease risk. The prescription of lipid-lowering medication and/or ASA was used as a proxy for CHD risk awareness and CHD prevention.

**ECG analysis**

Standard 12-lead ECGs were recorded at the health care centres according to clinical practice and all ECGs were analysed and classified by a cardiologist (KB) using the Novacode criteria measurement and classification system [165]. The examiner was blinded to clinical information.

ECG abnormalities were divided into major and minor abnormalities and a hierarchical categorisation was used where patients with only minor ECG abnormalities were classified as having minor abnormalities; patients with both minor and major abnormalities were classified as having major abnormalities. Patients without minor or major ECG abnormalities were classified as having marginal/absent abnormalities and their ECG was considered normal. The procedure has been described previously and both minor and major baseline ECG abnormalities were strongly associated with CVD, CHD, and most strongly with CHD death [166].

**Paper IV**

**Design and study participants**

This was a retrospective observational cross-sectional study of 19,382 (M/F 11,115/8,267) patients with type 2 diabetes aged 30–70 in the NDR. All patients were reported by a primary health care provider in 2003–2008, three years after a diabetes diagnosis. Patients with known CHD (n=3,556) or missing data for CHD (n=2,968) were excluded. The epidemiological definition of type 2 diabetes used in this study was: a patient treated with diet or oral hypoglycaemic agent (OHA) only and aged ≥30 years at onset of diabetes, or a patient treated with insulin alone or in combination with OHA and aged ≥40 years at onset of diabetes. Diabetes duration of three years was chosen as a marker for early achievement of treatment goals since it would permit patients and health care professionals to undertake interventional measures against CVD risk factors.

Laboratory analyses were carried out at local quality-assured laboratories. HbA1c values were converted to the Diabetes Control and Complications Trial (DCCT) standard values using the formula: HbA1c (DCCT) = 0.923 × HbA1c.
National guidelines were introduced in 1999 and treatment goals for glycaemia, blood pressure and lipids were HbA1c < 7.3%, BP ≤ 140/85 mm Hg, plasma total cholesterol < 5.0 mmol/L, plasma LDL cholesterol < 3.0 mmol/L. European guidelines, with lower treatment goals: HbA1c ≤ 6.1%, BP < 130/80 mm Hg, plasma total cholesterol < 4.5 mmol/L, plasma LDL cholesterol < 2.5 mmol/L were introduced in 2003 and were cited in the treatment recommendations of the Swedish Medical Products Agency in 2006 and hence might have influenced diabetes care in Sweden too [88, 138].

10-year CHD risk

Absolute 10-year risk of CHD, defined as the occurrence of fatal or non-fatal MI or sudden death, presented as the UKPDS risk engine version 2.0 was calculated for patients with all variables included in the equation, i.e. age, diabetes duration, smoking status, HbA1c, systolic blood pressure, total cholesterol, and HDL cholesterol [168]. Modifiable 10-year CHD risk was defined as a patient’s predicted 10-year CHD risk in excess of the risk (optimal 10-year CHD risk) for a non-smoking diabetes patient of the same sex, age and diabetes duration with HbA1c 6.1%, systolic BP 130 mm Hg, total cholesterol 4.5 mmol/L, and HDL cholesterol 1.0 mmol/L in men and 1.2 mmol/L in women (European treatment goals) [88]. The modifiable risk was calculated for each patient using the formula [(absolute 10-year CHD risk – optimal 10-year CHD risk) / optimal 10-year CHD risk] × 100 as described in the REACH OUT study [169].

Subgroup with initial and follow-up data

In order to enable the study of changes and interventions between diagnosis and follow-up within three years, a subgroup was created within the study population. Patients lacking initial data from the year of diabetes diagnosis were excluded. Patients with missing values for one or more of the variables used in calculating the UKPDS risk engine CHD estimates were also excluded. In 4,293 (M/F 2,460/1,833) patients with reported data in the year of a diabetes diagnosis and two (1,913, M/F 1,135/778) or three (2,380; M/F 1,325/1,055) years after diagnosis (follow-up), changes and interventions were evaluated. Because data from the year of diagnosis was mandatory, patients were diagnosed in 2003–2006.

Statistical analyses

Data are presented as proportions, mean value ± SD, and 95% confidence interval (95% CI) (paper I, III and IV).

The differences in proportions were tested with a Chi-squared test (paper I, III, and IV).

Differences between mean values were tested with Student’s t-test (paper III and IV). Linear regression (paper I) and one-way ANOVA (paper I and IV) were used to evaluate trends in mean values. Effects on means and interaction
were analyzed with a univariate analysis of variance (paper I). Paired-samples-
T-test was used for testing the differences between mean values in the subgroup
of patients with initial and follow-up data (paper IV). Two-sided significance
tests were used throughout. A difference was regarded as statistically significant
when $P<0.05$.

SPSS 13.0 in paper I, SPSS 15.0 in paper III, and PASW Statistics 18 in paper
IV (SPSS Inc, Chicago, IL) were used for statistical calculations.

**Ethical considerations**

All participants in paper I, II and III gave their informed consent to study
participation. The patients in paper IV gave their consent to be included in the
Swedish National Diabetes Register (NDR).

In paper I, III, and IV, registry data were used and in paper III additional data
were retrieved from medical records and no additional tests were performed.
All data handling procedures and analyses were conducted using an anonymous
data set and no contact was made with the participants. The possibility of vi-
olating the subject’s integrity must be considered to be low. In addition, public
and professional presentation of the results of the papers could be beneficial
to diabetic patients in future care.

Study I, II and III were approved by the Research Ethics Committee of the
Medical Faculty, Umeå University, Sweden and study IV by the Regional ethical
review board in Göteborg, Sweden.
RESULTS

The effectiveness of the introduction of treatment goals for dyslipidaemia in patients with type 2 diabetes
(Paper I)

Nine hundred and seventy-one, M/F 590/381, of 59,338 (1.6%) participants in the VIP in 1995–2004 reported having been diagnosed with diabetes. The prevalence of known diabetes in the study population increased between Periods I and II from 1.4% in 1995–1999 to 1.8% in 2000–2004 (P < 0.01), and was slightly higher in men than in women (P < 0.001).

There was a marked decrease in cholesterol levels in both men, 5.69 (±1.21) mmol/L vs. 4.99 (±1.00), and women, 5.97 (±1.20) vs. 5.20 (±1.00), with diabetes between Period I and Period II (P < 0.001 for both). An increasing proportion of diabetic patients, both men and women, reached the target level of fP-total cholesterol < 5 mmol/L. This proportion was greater among men than women, both in Period I, 25.8% vs. 16.2% (P < 0.05), and in Period II, 52.3% vs. 40.5% (P < 0.01).

In 1995–1999, the proportion of patients with type 2 diabetes on lipid-lowering agents was greater among men, 12.8%, than among women, 5.0% (P < 0.01), while no gender difference in treatment was found in 2000–2004, M/F 26.8%/23.2%. The total proportion of diabetic patients receiving lipid-lowering agents increased more than twofold during the observed period (P < 0.001).

As shown in Table 4, cholesterol levels were significantly lower in diabetic patients, both patients on lipid-lowering drugs and patients not on lipid-lowering drugs, than in non-diabetic participants after the introduction of new guidelines.

Table 4. Total cholesterol levels in the VIP 1995-2004 distributed by study period and diabetes status.

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Diabetes</td>
<td>Non-diabetes</td>
</tr>
<tr>
<td></td>
<td>(n=434)</td>
<td>(n=28619)</td>
</tr>
<tr>
<td>fP-total cholesterol (mmol/L) in all patients</td>
<td>5.79(±1.21)</td>
<td>5.79(±1.15)</td>
</tr>
<tr>
<td>fP-total cholesterol (mmol/L) in LLD-treated patients</td>
<td>5.99(±1.90)</td>
<td>5.52(±1.19)*</td>
</tr>
<tr>
<td>fP-total cholesterol (mmol/L) in patients not on LLD</td>
<td>5.77(±1.12)</td>
<td>5.79(±1.15)</td>
</tr>
<tr>
<td>On lipid lowering drug (LLD) (%)</td>
<td>9.9</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Data given are proportions (%) and mean values (±SD).
* = p<0.05, †= p<0.01, ‡ = p<0.001 indicates differences between diabetes and non-diabetes patients.
In Figures 6A and B, the mean total cholesterol, including a 95% confidence interval in the different cross-sectional study groups, is displayed, and the trend of lowered cholesterol levels in men and women both with and without a diabetes diagnosis is obvious. Linear regression analysis showed that this trend is highly significant in all four groups (men, diabetes Beta coefficient $-0.39$, $P<0.001$; men, non-diabetes Beta coefficient $-0.22$, $P<0.001$; women, diabetes Beta coefficient $-0.39$, $P<0.001$; women, non-diabetes Beta coefficient $-0.19$, $P<0.001$). The figures imply that there might be a stronger trend of lowered cholesterol levels in the group consisting of diabetic patients.

**Figure 6A.** Trend in mean (error bars 95% CI) total cholesterol 1995–2004 among women with (full line) and without (broken line) a diabetes diagnosis.
RESULTS

Figure 6B. Trend in mean (error bars 95% CI) total cholesterol 1995–2004 among men with (full line) and without (broken line) a diabetes diagnosis.

We performed a univariate analysis of variance that included variables in our study that might influence the trend of lowered cholesterol levels between 1995 and 2004: diabetes diagnosis, age, sex, BMI, smoking, lipid-lowering treatment, and physical exercise. Age and sex were found to be major influential factors and thus the results were divided by sex and age. Both the introduction of “diabetes diagnosis” and “lipid-lowering treatment” into the univariate analysis showed significant influence on mean total cholesterol levels, while smoking, BMI and physical activity did not.

We calculated the difference in total cholesterol levels between period II and period I in each age and sex group (Figure 7). The mean cholesterol levels were lower in period II and there was a significant difference between diabetic and non-diabetic patients in the oldest group with further lowered cholesterol levels in the diabetic patients group. The lack of differences in mean total cholesterol levels in the younger age groups was probably due to low power in these age groups.
Figure 7. Differences in mean total plasma cholesterol (mmol/L) period II (2000–2004) compared to period I (1995–1999) among men and women in different age groups with diabetes (filled bars) and without a diabetes diagnosis (open bars).

GPs’ experiences regarding treatment practice in type 2 diabetes with specific focus on the prevention of cardiovascular disease
(Paper II)

The overall theme was “dilemmas” encountered by GPs in their treatment practice for patients with type 2 diabetes. Five main dilemma categories were identified. The identified categories were explored in relation to difficulties in achieving treatment goals in clinical guidelines for the prevention of CVD.

The first dilemma category related to labelling someone who feels healthy as ill. GPs in all groups expressed concerns over the fact that health surveys and random blood glucose testing identify patients who feel healthy as having a chronic, potentially life-threatening, illness, i.e. type 2 diabetes. GPs were very much aware of the elevated risk of CVD and would also identify patients at high risk of CVD even without a diabetes diagnosis, i.e. obese patients, smokers, and patients with hypertension, and expressed concern about the absence of action against these major health problems taken by society. However, in person, GPs considered the task of putting a diabetes label on a subjectively healthy patient uncomfortable. This particular dilemma also included difficulties in motivating subjectively healthy patients to undergo lifestyle changes and/or take medication. This was discussed in contrast to patients who see their doctor for symptoms or complications relating to their diabetes who were easier to treat.
The second dilemma category, to frighten or comfort the patient, included difficulties in communicating a diabetes diagnosis and its consequences. This was something that had to be dealt with carefully to retain the patient’s trust. GPs discussed the need both to frighten and comfort the patient. It may be necessary to frighten the patient in order for him or her to take the advice of the physician seriously. On the other hand, GPs clearly interpreted diabetes as something close to a ‘death sentence’ and wanted to spare the patient from this knowledge. The dilemma of comforting or frightening included an uncertainty as to how much the patient should be told about the disease.

The third dilemma category, to take responsibility for the care or not, included ambivalence among GPs concerning their role and responsibilities in diabetes care in relation to patients and co-workers such as diabetes nurses. Providing the diabetic patient with sufficient information enabling him or her to take necessary actions was regarded as the physician’s responsibility by the GPs. However, many GPs also said that the ultimate responsibility for the outcome of cardiovascular prevention lies with the patient himself/herself. Between these two extremes – the start and end point of the course of diabetes care – the GPs had different approaches in relation to the patient. It was clear from discussions that some GPs regarded themselves as responsible for the care and treatment of the patient and would intervene when necessary. They would act as active coaches and prescribe adequate medical treatment when needed to prevent cardiovascular complications. Others described their role as providing adequate information – then leaving it to the patient to decide whether to comply or not. The GP would accompany the patient along the road and provide counselling – act as sounding board – when contacted by the patient. Some GPs said that the diabetes care at their clinic depended on the diabetes nurse rather than on their own activities and that they would support the nurse when asked to do so.

The fourth dilemma category was a conflict between lifestyle changes and drug treatment. GPs were ambivalent as regards drug treatment early in the course of diabetes. They said that patients might refrain from making necessary changes in lifestyle such as increased physical activity, diet, weight loss, and smoking cessation if they were given the impression that drugs were an effective alternative. During the course of diabetes, GPs repeatedly dealt with test results diverging from treatment goals. Lifestyle changes were described as the optimal alternative in this situation but finally, according to most GPs, diabetic patient would receive several pharmaceutical drugs. In some GPs’ opinion this was inevitable, though not desirable. GPs asked for collegial support, case discussions in the practice setting, and consultations with diabetes specialists at the hospital as means to improve treatment in difficult cases.

The interviews contained stories about exceptional patients, who changed their lifestyle in a way that altered their glucose tolerance to normal. These miraculous patients, who had followed their doctor’s advice to the letter, served
as a relief. They seemed, on one hand, to support the GPs’ opinion of the importance of lifestyle changes also in other patients and, on the other hand, to support the GPs’ hesitation relating to drug treatment.

The fifth dilemma was to integrate science into reality. All focus groups agreed that the prevention of cardiovascular disease in diabetic patients by treating lipids, blood pressure, and glucose levels was important. However, different opinions on guidelines for type 2 diabetes were expressed. The very existence of guidelines was not openly questioned, but scepticism as well as strong beliefs relating to the beneficial effect of such guidelines was revealed. The need to individualize and adapt goals depending on which patient you are treating was strongly expressed in all groups. In this, great scepticism about specific treatment goals in guidelines was disclosed; it was felt that, in reality, such goals must be adjusted in order to be more achievable. The focus groups did not discuss how to involve the patient in the decision-making process.

The patient’s own sense of well-being was considered very important, and several GPs described this as their primary treatment goal where side effects of medication could interfere. The patient’s well-being could also be threatened if the GP focused on treatment goals instead of focusing on “meeting” the individual patient.

**Screening for microvascular and coronary heart disease in newly diagnosed diabetic patients**

(Paper III)

The study comprised 201, M/F 122/79, patients, mean age 55.9,±6.5, years, of whom 184 patients (91.5%) were diagnosed with type 2 diabetes and 17 (8.5%) with unclassified diabetes. All patients were diagnosed by screening and thus early on in the disease, which was reflected by a low mean HbA1c, 7.4, ±1.9,%, at diagnosis.

**Screening for microvascular complications**

The vast majority of the patients had been screened for albuminuria (Table 5). In total, 24 (13%, M/F 18/6) patients had an abnormal albumin excretion. This was only commented on in the medical records of six of the patients. Most of the patients had also been referred for retinal photo with a resulting low frequency of retinopathy, all of which were simplex, 13 (8%, M/F 11/2) patients. Just over half the patients were screened for neuropathy by using a tuning fork or monofilament or both, and a minority, 19 (17%, M/F 11/8) patients, showed pathological findings according to notes in their medical records.
Table 5. Frequency of methods for screening for coronary heart disease and microvascular complications in 201 screening detected diabetic patients.

<table>
<thead>
<tr>
<th>Method</th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuminuria screening</td>
<td>112(92%)</td>
<td>73(92%)</td>
<td>92%</td>
<td>88.3–95.8</td>
</tr>
<tr>
<td>Retinal photo</td>
<td>96(79%)</td>
<td>65(83%)</td>
<td>80%</td>
<td>74.6–85.6</td>
</tr>
<tr>
<td>Peripheral nerve exam</td>
<td>65(55%)</td>
<td>48(61%)</td>
<td>56%</td>
<td>49.4–63.1</td>
</tr>
<tr>
<td>ECG screening</td>
<td>47(39%)</td>
<td>40(51%)</td>
<td>43%</td>
<td>36.4–50.1</td>
</tr>
<tr>
<td>Normal</td>
<td>73%</td>
<td>78%</td>
<td>76%</td>
<td></td>
</tr>
<tr>
<td>Minor abnormalities</td>
<td>16%</td>
<td>11%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Major abnormalities</td>
<td>11%</td>
<td>11%</td>
<td>11%</td>
<td></td>
</tr>
</tbody>
</table>

Data given are numbers (n) and proportions (%). Proportions of albuminuria screening methods and ECG findings are of patients screened.

* = p<0.05, † = p<0.01, ‡ = p<0.001 indicates differences between men and women.

Screening for coronary heart disease and secondary prevention

An ECG was performed in a minority of patients (table 5) and 94% of these ECGs were retrieved. Twenty, M/F 12/8, patients had minor or major ECG abnormalities. The majority, 15/20, had no clinical CVD diagnosis. Five out of twenty had a recorded history of CVD (two had prior MIs and three were diagnosed with CHD, stroke, and heart failure, respectively, during the follow-up time).

Of the 15 patients with minor or major ECG abnormalities but without known CVD, 6 (40%) were treated with lipid-lowering medication and 6 (40%) received ASA treatment.

No cardiovascular risk score had been used in any of the patients.

Clinically diagnosed CHD and secondary prevention

Nineteen, M/F 13/6, of the patients were diagnosed with CHD according to their medical records. Patients with a diagnosis of CHD were to a greater extent treated with lipid-lowering medication (74%) and ASA (95%) compared to those without CHD (lipid-lowering medication 35%; ASA 36%, P<0.01 for both).

Comparison of microvascular and CHD screening

A greater proportion of patients were screened for retinopathy and nephropathy than for CHD (table 5). There was no difference in the proportions being screened for CHD or neuropathy.
Time trends in treatment goal achievements and 10-year CHD risk at three years diabetes duration in 2003–2008

(Paper IV)

Time trends in risk factor levels and treatment goal achievements

As can be seen in table 6, there were no differences in age or sex distribution over the years. There was a trend of increasing BMI ($P<0.05$) but also a temporal trend of lowered HbA1c, systolic and diastolic blood pressure, and lipid levels ($P<0.001$ for all) (Table 6). The trend in lowered HbA1c, blood pressure, and lipid levels were found in both men and women, but women had significantly lower diastolic blood pressure and higher plasma total cholesterol than men (data not shown).

In parallel with lowered HbA1c, there was a trend of increase in the use of oral hypoglycaemic agents (OHA) (Table 6). There was also a trend of increased use of antihypertensives, but about one quarter of hypertensive patients were not on medical treatment (Table 6). In spite of the trend of increased use of lipid-lowering drugs (LLD), a majority of patients above national treatment targets were not treated with LLD (Table 6).

The proportion of patients who were smokers did not change during the study period (Table 6).

In 2008, 23.9% (M/F 24.7%/22.8%) of the patients had glycaemic as well as blood pressure and lipid levels within national treatment goals, while 1.3% (M/F 1.3%/1.4%) patients had glycaemic as well as blood pressure and lipid levels within European treatment goals (data not shown).
RESULTS

Table 6. Clinical characteristics and treatment goal achievements in patients at 3 years duration of type 2 diabetes in each survey year 2003–2008.

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (M/F)</td>
<td>(969/700)</td>
<td>(1454/1067)</td>
<td>(1680/1239)</td>
<td>(2186/1596)</td>
<td>(2386/1887)</td>
<td>(2440/1778)</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.3</td>
<td>58.1</td>
<td>58.3</td>
<td>58.5</td>
<td>58.4</td>
<td>58.5</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>(579.5-58.7)</td>
<td>(579.5-58.4)</td>
<td>(579.5-58.6)</td>
<td>(582.5-58.7)</td>
<td>(586.5-58.7)</td>
<td>(582.5-58.7)</td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.2</td>
<td>7.2</td>
<td>7.2</td>
<td>7.2</td>
<td>7.2</td>
<td>7.2</td>
<td></td>
</tr>
<tr>
<td>HbA1c &lt; 7.3 (%)</td>
<td>(n=19163)</td>
<td>(n=19163)</td>
<td>(n=19163)</td>
<td>(n=19163)</td>
<td>(n=19163)</td>
<td>(n=19163)</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>24.4</td>
<td>24.7</td>
<td>24.7</td>
<td>24.7</td>
<td>24.7</td>
<td>24.7</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>(n=18300)</td>
<td>(n=18300)</td>
<td>(n=18300)</td>
<td>(n=18300)</td>
<td>(n=18300)</td>
<td>(n=18300)</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>&lt; 3.0 mmol/L</td>
<td>(5.1-5.1)</td>
<td>(5.0-5.1)</td>
<td>(5.0-5.1)</td>
<td>(5.0-5.1)</td>
<td>(5.0-5.1)</td>
<td>(4.9-5.0)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>&lt; 2.5 mmol/L</td>
<td>(25.3-30.3)</td>
<td>(28.3-32.5)</td>
<td>(31.6-35.5)</td>
<td>(33.4-37.0)</td>
<td>(34.1-37.5)</td>
<td>(35.4-38.9)</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>22.0</td>
<td>19.2</td>
<td>19.3</td>
<td>17.8</td>
<td>19.0</td>
<td>19.2</td>
<td>NS</td>
</tr>
<tr>
<td>OHA and/or insulin (%)</td>
<td>(19.9-24.1)</td>
<td>(17.6-20.8)</td>
<td>(17.8-20.8)</td>
<td>(16.5-19.1)</td>
<td>(17.8-20.2)</td>
<td>(18.6-20.5)</td>
<td>NS</td>
</tr>
<tr>
<td>% of patients with HbA1c &gt; 7.3 not on OHA and/or insulin (%)</td>
<td>(13.4-17.6)</td>
<td>(14.6-22.2)</td>
<td>(12.2-17.6)</td>
<td>(13.6-17.6)</td>
<td>(9.1-17.6)</td>
<td>(7.4-11.6)</td>
<td>(7.1-11.6)</td>
</tr>
<tr>
<td>Antihypertensive drugs (%)</td>
<td>(10.3-16.5)</td>
<td>(11.8-17.4)</td>
<td>(9.6-14.7)</td>
<td>(11.1-16.0)</td>
<td>(7.4-11.6)</td>
<td>(7.1-11.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Lipid lowering drugs (%)</td>
<td>(35.3-40.4)</td>
<td>(39.5-43.4)</td>
<td>(40.4-43.4)</td>
<td>(43.4-49.2)</td>
<td>(49.2-54.3)</td>
<td>(50.0-54.3)</td>
<td>NS</td>
</tr>
<tr>
<td>% of patients with total cholesterol ≤ 5.0 mmol/l not on LDL (%)</td>
<td>(67.7-65.5)</td>
<td>(65.0-64.0)</td>
<td>(61.1-57.8)</td>
<td>(57.8-53.0)</td>
<td>(53.0-60.1)</td>
<td>(51.7-56.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Absolute 10-year CHD risk (%) in patients with all data for UKPDS risk score (%)</td>
<td>(15.9-16.4)</td>
<td>(14.4-15.3)</td>
<td>(14.3-15.0)</td>
<td>(13.8-14.5)</td>
<td>(13.9-14.6)</td>
<td>(14.5-15.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Optimal 10-year CHD risk (%)</td>
<td>(12.5-12.9)</td>
<td>(12.2-12.7)</td>
<td>(12.3-12.8)</td>
<td>(12.2-12.6)</td>
<td>(12.4-12.9)</td>
<td>(12.4-12.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Modifiable 10-year CHD risk (%)</td>
<td>(27.7-26.5)</td>
<td>(22.9-17.5)</td>
<td>(19.8-22.4)</td>
<td>(22.4-24.4)</td>
<td>(24.1-28.9)</td>
<td>(20.6-25.2)</td>
<td>(19.7-21.7)</td>
</tr>
</tbody>
</table>

Data given are number, means, proportions (%), and 95% confidence interval (95%CI). HbA1c values are DCCT-standardized. BP, blood pressure. LDL, lipid lowering drugs. Optimal 10-year CHD risk (%), absolute 10-year CHD risk if HbA1c 6.1, systolic BP 130, total cholesterol 4.5, HDL cholesterol 1.0 in men and 1.2 in women. Modifiable 10-year CHD risk, excess 10-year risk of CHD when absolute risk was compared to optimal risk. * = p<0.05, † = p<0.01, ‡ = p<0.001 for trend.
RESULTS


In 13,850 patients with data allowing calculation of absolute 10-year risk of CHD, the absolute 10-year risk of CHD decreased during the study period (Table 6). The absolute 10-year risk of CHD was about twice as high in men than in women and decreased in both sexes (Figure 8A). The remaining modifiable risk was about 41% in men and 64% in women ($P<0.001$) in patients with absolute risk above the mean value (Figure 8B). Trend analysis showed lowered modifiable risk in men whose absolute 10-year CHD risk was below or above mean absolute risk ($P<0.001$ for both) and in women with absolute 10-year CHD risk below mean absolute risk ($P<0.05$), but not in women with absolute 10-year CHD risk above mean absolute risk (Figure 8B).

![Figure 8A. Time trends in absolute (mean value, 95% CI bars) 10-year risk of CHD 3 years after diagnosis in men (full line, triangles) and women (broken line, circles) with type 2 diabetes 2003–2008.](image-url)
Effects of treatment on 10-year CHD risk in a subgroup with initial and follow-up data

The patients in the subgroup with initial and follow-up data did not differ from the whole study population in age (58.7, 95%CI 58.4–58.9) vs. 58.4, 95%CI 58.2–58.5) nor in proportions between sexes (M/F 57.3%/42.7% vs. M/F 57.3%/42.7%). There were, however, differences in results between the subgroup and the whole study population. The overall proportions at follow-up for the subgroup vs. the whole study population within national targets for HbA1c, blood pressure, and total cholesterol were 81.9%, 80.7–83.0, vs. 78.3%, 77.7–78.9, 64.6%, 63.1–66.1, vs. 61.9%, 61.2–62.6, and 55.3%, 53.8–56.8 vs. 51.1%, 50.3–51.8, i.e. larger proportions of patients in the subgroup were within target levels for these CVD risk factors compared to the whole study population. The proportion of patients smoking at follow-up did not differ between the subgroup vs. the whole study population (18.0%, 95%CI, 16.8–19.2 vs. 19.1%, 95%CI, 18.5–19.7).
The numerical lowering of HbA1c between year of a diabetes diagnosis and follow-up was small, indicating intervention taking place already in the first year. This was supported by our finding that 41.2% of the patients were on antidiabetic drugs in the first year (Table 7). Medical treatment had also increased at follow-up and treatment with OHA, insulin as well as combinations of insulin and OHA increased (data not shown). However, there was no tendency of increase in the proportion of patients reaching an HbA1c of ≤ 6.1 mmol/L at follow-up.

Half of the patients were treated with antihypertensive drugs already in the year of diabetes diagnosis, and the proportion increased until follow-up. Two thirds of the patients achieved national treatment goals at follow-up and there was also an increase in the proportion that fell within the lower European targets.

Total and LDL cholesterol, but not HDL cholesterol, levels improved until follow-up. About a quarter of the patients were treated with LLD in the year of diagnosis and at follow-up the proportion on LLD treatment was about 50%.

In contrast to the improvements in glycaemic, blood pressure, and lipid levels between diagnosis and follow-up, the frequency of daily smoking did not improve. BMI remained unaltered in men, and improved slightly in women.

Absolute 10-year risk of CHD was about twice as high in men as in women (Table 7). There was a small but significant increase in absolute CHD risk between the year of diagnosis and follow-up. Reduced levels of HbA1c, systolic blood pressure, and total cholesterol, but not HDL cholesterol or smoking, influenced CHD risk. This improved the modifiable 10-year CHD risk in both men and women. Our results show that about 20% of the excess risk, compared to an optimally treated diabetic patient of the same age and diabetes duration, could be modified by risk factor intervention. In addition, the proportion of patients with the highest 10-year CHD risk, ≥ 30%, did not alter between diagnosis and follow-up.
Table 7. Risk factor levels and 10-year CHD risk in T2DM patients in follow-up subgroup.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>2460 (57.3)</td>
<td>1833 (42.7)</td>
<td>4293</td>
</tr>
<tr>
<td>Age at follow-up</td>
<td>58.1</td>
<td>59.5</td>
<td>58.7</td>
</tr>
<tr>
<td>(years)</td>
<td>(57.8-58.5)</td>
<td>(59.1-59.8)</td>
<td>(58.4-58.9)</td>
</tr>
<tr>
<td>Diabetes duration at follow-up (years)</td>
<td>2.5</td>
<td>2.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Follow-up</td>
<td>15.8</td>
<td>1833 (42.7)</td>
<td>2460 (57.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk factor levels</th>
<th>Year of diagn</th>
<th>Follow-up</th>
<th>Year of diagn</th>
<th>Follow-up</th>
<th>Year of diagn</th>
<th>Follow-up</th>
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<tbody>
<tr>
<td>BMI (kg/m2)</td>
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<tr>
<td></td>
<td>(30.0-30.5)</td>
<td>(30.0-30.5)</td>
<td>(31.0-31.6)</td>
<td>(30.7-31.3)</td>
<td>(30.5-30.9)</td>
<td>(30.4-30.8)</td>
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<tr>
<td>HbA1c (%)</td>
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<tr>
<td></td>
<td>6.8 (6.7-6.9)</td>
<td>6.7† (6.6-6.7)</td>
<td>6.8 (6.7-6.8)</td>
<td>6.6† (6.5-6.6)</td>
<td>6.8 (6.7-6.8)</td>
<td>6.7† (6.6-6.7)</td>
</tr>
<tr>
<td>HbA1c &lt; 7.3%</td>
<td></td>
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<td></td>
<td>76.3 (74.6-78.0)</td>
<td>79.9 (78.3-81.5)</td>
<td>79.7 (77.8-81.5)</td>
<td>84.5 (82.7-86.1)</td>
<td>77.7 (82.7-86.1)</td>
<td>81.9</td>
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<tr>
<td>HbA1c ≤ 6.1%</td>
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<tr>
<td></td>
<td>28.8 (26.9-30.6)</td>
<td>27.8 (25.9-29.5)</td>
<td>27.8 (25.7-29.9)</td>
<td>29.3 (27.2-31.4)</td>
<td>28.4 (27.0-29.7)</td>
<td>28.4</td>
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<tr>
<td>Systolic BP (mmHg)</td>
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<td></td>
<td>137.5 (136.7-138.1)</td>
<td>135.5† (134.8-136.1)</td>
<td>137.7 (136.9-138.5)</td>
<td>134.1 (134-13-135.5)</td>
<td>137.0 (130-138.1)</td>
<td>135.2†</td>
</tr>
<tr>
<td>BP ≤ 140/85 (%)</td>
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<td></td>
<td>57.4 (55.4-59.3)</td>
<td>62.9 (61.0-64.8)</td>
<td>58.2 (55.9-60.5)</td>
<td>64.7 (64.7-69.0)</td>
<td>62.0 (56.2-59.2)</td>
<td>63.1 (66.1)</td>
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<tr>
<td>BP &lt; 130/80 (%)</td>
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<td>15.8 (14.3-17.2)</td>
<td>19.3 (17.7-20.9)</td>
<td>18.9 (17.0-20.7)</td>
<td>23.7 (21.7-25.7)</td>
<td>17.1 (15.9-18.2)</td>
<td>21.2</td>
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<td>Diastolic BP (mmHg)</td>
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<tr>
<td></td>
<td>81.8 (81.8-82.2)</td>
<td>80.2† (79.8-80.6)</td>
<td>79.9 (79.4-80.3)</td>
<td>77.8 (77.3-80.0)</td>
<td>81.0 (80.6-81.3)</td>
<td>78.8 (79.9)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.2</td>
<td>4.8†</td>
<td>5.5</td>
<td>5.0†</td>
<td>5.4</td>
<td>4.9†</td>
</tr>
<tr>
<td>&lt; 5.0 mmol/L (%)</td>
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<tr>
<td></td>
<td>42.2 (40.2-44.2)</td>
<td>59.4 (57.4-61.8)</td>
<td>32.0 (29.8-34.1)</td>
<td>47.5 (45.2-52.2)</td>
<td>36.3 (33.9-39.3)</td>
<td>55.3</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.2</td>
<td>4.7-4.9</td>
<td>5.4-5.6</td>
<td>5.0-5.1</td>
<td>5.3-5.4</td>
<td>4.8-4.9</td>
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<tr>
<td>&lt; 4.5 mmol/L (%)</td>
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<td>22.6 (20.9-24.3)</td>
<td>37.2 (35.2-39.1)</td>
<td>16.6 (14.9-18.4)</td>
<td>29.7 (27.9-31.2)</td>
<td>18.8 (18.2-21.3)</td>
<td>31.2 (36.5-35.5)</td>
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<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.1</td>
<td>2.8</td>
<td>3.3</td>
<td>2.9†</td>
<td>3.2</td>
<td>2.8†</td>
</tr>
<tr>
<td>&lt; 3.0 mmol/L (%)</td>
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<tr>
<td></td>
<td>46.9 (44.8-48.9)</td>
<td>63.1 (61.2-65.1)</td>
<td>37.9 (35.6-40.2)</td>
<td>56.7 (56.1-61.3)</td>
<td>41.5 (44.1-46.6)</td>
<td>59.6 (59.6-62.8)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>24.6</td>
<td>38.8</td>
<td>20.6</td>
<td>35.7</td>
<td>22.9</td>
<td>37.5</td>
</tr>
<tr>
<td>&lt; 2.5 mmol/L (%)</td>
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<td>1.2 (1.2-1.2)</td>
<td>1.2 (1.1-1.2)</td>
<td>1.3 (1.3-1.4)</td>
<td>1.3 (1.3-1.4)</td>
<td>1.2 (1.2-1.3)</td>
<td>1.3 (1.2-1.3)</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>18.2 (16.6-19.8)</td>
<td>17.3 (15.8-18.9)</td>
<td>20.2 (18.2-22.1)</td>
<td>171.20.8)</td>
<td>178.20.3)</td>
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</tr>
<tr>
<td>Antidiabetic drugs (%)</td>
<td>43.5</td>
<td>65.8</td>
<td>38.1</td>
<td>60.1</td>
<td>41.2</td>
<td>63.4</td>
</tr>
<tr>
<td>Antihypertensive drugs (%)</td>
<td>47.9</td>
<td>63.7</td>
<td>53.6</td>
<td>67.2</td>
<td>50.3</td>
<td>65.2</td>
</tr>
<tr>
<td>Lipid lowering (%)</td>
<td>45.8-49.9 (61.7-65.6)</td>
<td>51.3-56.0 (65.0-69.4)</td>
<td>56.4 (54.1-58.7)</td>
<td>27.4 (26.0-28.8)</td>
<td>51.2-54.3</td>
<td></td>
</tr>
<tr>
<td>Absolute 10-year CHD risk (%)</td>
<td>16.9</td>
<td>17.6†</td>
<td>9.5</td>
<td>9.6</td>
<td>13.7</td>
<td>14.2†</td>
</tr>
</tbody>
</table>

RESULTS

Data given are number, means, proportions (%) and 95% confidence interval (95%CI). HbA1c values are DCCT-standardized.

* = p<0.05, † = p<0.01, ‡ = p<0.001 indicates differences between values year of diagnosis and at follow up. Absolute 10-year CHD risk (%), absolute 10-year CHD risk calculated using the UKPD risk engine, version 2.0. Optimal 10-year CHD risk (%), absolute 10-year CHD risk if HbA1c 6.1, systolic BP 130, total cholesterol 4.5, HDL cholesterol 1.0 in men and 1.2 in women. Modifiable 10-year CHD risk, excess 10-year risk of CHD when absolute risk was compared to optimal risk.
DISCUSSION

Methodological considerations

Study designs

The aim of Paper I was to analyse whether the new national guidelines that were introduced in 1999 had improved cholesterol levels in the diabetic patient population. Most clinical epidemiological studies of guideline implementation are derived from selected clinical populations. The population-based VIP health survey provided scientists the opportunity to look at cholesterol levels in people with diabetes, rather than selected clinical samples of diabetic patients. The study design of “before” and “after” is questionable as the introduction of new guidelines is often preceded by research results that may have been discussed among health care professionals and may have lead to changes in treatment practice even before new guidelines were introduced. This can be exemplified by the presentation of results from the UKPDS that preceded the development of the 1999 national guidelines. The assumed gradual change in treatment practice was dealt with by summarising and comparing data from five years before and after the new guidelines were introduced. The cross-sectional design does not allow for any conclusions on cause and effect. However, since trends in cholesterol levels in the diabetic patients were compared to secular trends, the improved levels in the second time period could be interpreted as diabetes-specific in line with guidelines.

The aim of Paper II was to explore GPs’ experiences of CVD prevention in diabetes care. The authors chose a focus group approach as it would allow interaction between GPs which would reveal dimensions of understanding that could have been lost if individual interviews had been used [170]. By using the focus group approach it is also possible to examine how knowledge and ideas operate in a given context and it is useful in exploring attitudes – issues that were included in the aim of the paper. We chose to interview experienced GPs and the homogeneity within the groups served to deepen the discussions, thus exploring mutual experiences further. Recruitment difficulties led to the groups being smaller than initially intended. Between four and twelve members per group has been recommended [171]. However, the gathered information was plentiful. The choice of an experienced focus group moderator who was also a nurse, but without any involvement in diabetes care could have facilitated the discussions. The possibility of individual voices of dissent being silenced in a group must be recognized, and this problem was counteracted by encouragement from the moderator.

The aim of Paper III was to assess if screening for CHD was performed as often as screening for microvascular complications. We had the opportunity to study a population-based sample of screening-detected patients with type 2 diabetes, which limited selection bias, but on the other hand limited the number of patients. Screening methods were defined in the Swedish national
guidelines and were registered in the computerised medical records which facilitated this study from 34 primary health care centres. The retrospective observational cross-sectional design does not allow interpretations of cause and effect but we noted lipid-lowering and ASA prescriptions as proxies for CHD attention.

Time trends in glycaemia, blood pressure and plasma lipid levels were studied in Paper IV and data in the NDR were used. The choice of three years as a definition of ‘short duration’ and the anticipation of interventional measures to be undertaken during that time could be questioned. However, an even shorter time for interventional measures could be advocated. The time period 2003–2008 was chosen since blood lipids were not reported in the NDR to any greater extent before 2003. CHD is the main cause of death in patients with type 2 diabetes and reducing CHD risk is the main aim of CVD risk factor intervention. Hence, calculating absolute and modifiable 10-year CHD risk and evaluating time trends seemed an appropriate illustration of primary intervention. We used the UKPDS risk engine model adjusted for single measurements of risk factors to avoid over-estimation of risk as described in the Appendix of the UKPDS 56 article [168]. Lifestyle interventions such as increased physical activity and dietary changes were not evaluated in our study but might have contributed to reduced risk.

Validity
The external validity of the diabetes population in Paper I may be questioned since the prevalence of known diabetes was unexpectedly low, 1.6%, 95% CI 1.5–1.7, among the participants aged 40–60 in the VIP. In another population-based survey from northern Sweden, MONICA, the prevalence of known diabetes in people aged 35–64 was 2.8%, 95% CI 1.8–3.8, in 1999 [15]. There might have been a bias in our diabetes population as well-aware and well-treated persons might refrain from participating in a health survey at their health care centre. Hence, the results may underestimate cholesterol lowering in diabetic patients in general, but the unaltered diabetes prevalence during the study period indicated that trends in improved cholesterol levels were valid also in the diabetic patient population in general. Self-report of physician-diagnosed diabetes and recall of drug treatment for well-defined chronic diseases have earlier been shown to be accurate which strengthens the interval validity of our study [172, 173]. Ideally, we would have liked to have had the opportunity to follow a large, population-based cohort and study changes and interventions, but even in such a study there might be problems with bias in follow-up attendance and external validity due to increased awareness among study participants. Sufficient internal validity in Paper I was supported by the use of quality-assured dry chemical methods for the analyses of plasma lipid levels. The great number of participating primary health care centres could jeopardize the validity of blood pressure and other examination results.
The recruitment of physicians for participation in the focus group interviews in Paper II was a challenge, also recognised by others [160]. One participant in one of the later groups made a revealing slip after the first focus group by asking “How did they do in the test?”. This question might well reflect that doctors were embarrassed being asked questions about clinical practice and guidelines and thus refrained from participation in order to avoid a possible knowledge test. Recruitment might hence have been biased towards participants being more self-secure and experienced and external validity, i.e. the transferability of our results to other GPs, could be questioned. In order to address this issue, the results have been presented at meetings with GPs in Västerbotten and also at a diabetologist meeting with doctors who are interested in diabetes as well as hospital specialists. In discussions at these meetings, the presented dilemmas seemed to be recognised and familiar among the physicians. The concept of trustworthiness also includes how well the categories and themes cover data [164]. The analysis of manifest and latent content in the interviews was illustrated by citations and an example of coding and categorisation of meaning units in Paper II to enable the reader to judge the credibility of the findings.

In Paper III we studied screening-detected diabetic patients in a population-based survey, which reduces the selection bias. A participation rate of 85%, as in the DIVE, also allows some generalisations of the results to newly diagnosed patients with type 2 diabetes in general. Studies based on medical records, however, have some limitations since the registration of important data and clinical considerations might differ or be omitted in spite of their presence in the consultation. In addition, it was not possible to assess the occurrence of lifestyle interventions in our study. On the other hand, it was possible to evaluate secondary prevention as prescriptions of medications were automatically registered in the computerised medical records. Bearing these strengths and limitations in mind, the internal and external validity of our findings concerning the screening frequency for CHD and microvascular disease was reasonably high. However, one must be careful when interpreting secondary preventive measures after ECG screening as the numbers were small. Also, the retrospective exploratory design does not allow conclusions of cause and effect.

In Paper IV, reported data in the NDR were used. There are some limitations that should be considered. First, about 60% of the estimated number of diabetic patients is reported in the NDR, even lower proportions in earlier years, and a selection bias could exist in that better managed patients are reported to a greater extent than less well-treated patients. The number of reported patients also differed between years in our study. Further, there were geographical differences in proportion of patients reported in the NDR that might reduce the representativeness of our results. LDL cholesterol levels in the cross-sectional part of the study should be treated with some caution due to missing values. However, there was no difference in missing values between men and women.
The internal validity of measurements was shown to be accurate in a regional study and there were also no systematic differences between registered and non-registered diabetic patients [174]. Regression dilution might influence estimates of differences between two measurements and hence overestimate improvements in risk in the studied subgroup.

The UKPDS Risk Engine’s ability to discriminate and predict 10-year CHD risk has been tested against clinical end-points in two British populations and the C-index for individuals with diabetes was 0.76 and 0.67 respectively for CHD risk, indicating acceptable discrimination [128, 129]. True CHD risk compared to predicted risk was 1.6:1 in patients in a hospital setting, but non-significantly 1.2:1 in newly diagnosed patients with type 2 diabetes in primary health care. Patients were up to 75 years old in both studies [128, 129]. Discrimination and predictive ability of CVD, but not CHD risk, by the UKPDS risk engine were evaluated in the EPIC-Norfolk cohort and the C-index was 0.76 but true CVD risk compared to predicted risk was 0.77:1, i.e. the risk was overestimated [135]. More recent data from the ADVANCE group also indicated an overestimation of 4-year CHD risk by the UKPDS risk engine [175]. However, about half the patients in the ADVANCE study were of Chinese origin, and an earlier test of the Framingham risk score showed a substantial overestimation of risk in a Chinese non-diabetic population [176]. The modifiable risk and trends in risk, used in our study, reduced the influence of incorrect estimates of absolute risk levels. The small difference in age at diagnosis between patients in our study, up to 70 years of age, and in the UKPDS cohort, up to 65 years of age, probably did not affect modifiable risk or trends in risk to any greater extent.

**Main findings**

Our findings in papers I and IV reflect a gradual progress in treatment goal achievements for the prevention of CVD in type 2 diabetes following the introduction of national guidelines in 1999. The gradual progress and achievements of blood pressure and lipid levels resemble those in the NHANES study in 1999–2000 [148]. In spite of the enhanced trend of cholesterol lowering following the introduction of the guidelines, only 25.3% of the participants with diabetes were treated with lipid-lowering drugs in 2000–2004 and 52% of diabetic patients with short duration of the disease in 2008 (papers I and IV). Out of known risk factors for CVD, hyperlipidaemia received the least intensive treatment compared to glycaemia and blood pressure during 2003–2008 (Paper IV). The treatment of hyperlipidaemia has substantial impact on CHD risk and our observed discrepancy between aims in guidelines and clinical practice could contribute to the remaining high CHD incidence in people with diabetes [43, 44, 98, 99]. Hyperlipidaemia was also the least intensively treated risk factor already in 1996–1997 [177].

An important finding is that the prevalence of risk factor treatment did not differ between men and women after the introduction of guidelines in 1999.
This is in line with the guidelines. The absence of gender differences in risk factor treatment was also supported by data from 229 primary health centres in Sweden [178].

Our findings in the subgroup with both initial and follow-up data on all variables included in the UKPDS equation indicated that these patients received more intervention than the whole population (Paper IV). However, similarities in BMI, smoking, and proportions treated with OHA, antihypertensive, and lipid-lowering drugs at follow-up in the subgroup and the whole population, implied that some conclusions could be drawn from the results. We found that during the first three years after a diabetes diagnosis substantial improvements in risk reduction were made. This was accomplished through multifactorial intervention against hyperglycaemia, hypertension and hyperlipidaemia. BMI remained mainly unaltered and we found no reduction in smoking.

Our findings of a trend during 2003–2008 of improved levels of HbA1c, systolic blood pressure, and total cholesterol, but not HDL cholesterol or smoking, also led to a weak trend of lowered absolute 10-year CHD risk and a calculated remaining modifiable CHD risk of about 20% in 2008. The estimated 10-year CHD risk in the year of diabetes diagnosis in Paper IV was similar to that in screening-detected diabetic patients in the ADDITION trial, 21% in men and 11% in women, recruited from 2001 to 2006 [179]. Lipid levels, blood pressure, and smoking are targets for further improvements. Improved intervention against these risk factors could also have an impact on the substantial remaining modifiable risk in both men and women with higher than average 10-year CHD risk demonstrated in Paper IV.

The problems within the consultation with diabetic patients that were described by the GPs in the focus group interviews in Paper II could contribute to the slow progress in improved treatment goal achievements and CVD risk factor levels. In spite of the GPs’ awareness of elevated CVD risk and the seriousness of a diabetes diagnosis, they experienced difficulties in motivating interventional measures in subjectively healthy diabetic patients. Patients who see the doctor for complications of their diabetes were described as easier to treat. Our findings in Paper III of a high prevalence of cardiovascular prevention in patients with clinically diagnosed CHD, but not in those with high CHD risk detected by screening, also support this notion. The task of treating conditions with definite symptoms was also described in an earlier study as easier than treating diabetes [180]. The GPs reluctance to communicate the consequences of type 2 diabetes could also negatively affect patients’ understanding and motivation to undertake life-style changes or comply with drug treatment. The expressed opinion in Paper II that CVD prevention with drugs could interfere with the doctor-patient relationship might also negatively affect CVD prevention if drawn to its conclusion. Also, the ambivalence among the GPs concerning their professional role and responsibilities could contribute to differences in treatment. The GPs in our study requested increased collegial support.
The apparent conflict between lifestyle changes and drug treatment, expressed by GPs in Paper II, has not been described previously. This opinion, combined with a perception of lifestyle changes as the optimal alternative, could lead to medical treatment being postponed and thus contribute to the revealed slow progress of improved risk factor levels.

Scepticism about treatment goals in guidelines was revealed in our study in Paper II. If GPs consider treatment goals as impossible to reach, this could affect the efforts to achieve them. It has been argued that the current treatment goals for type 2 diabetes as regards glycaemia, blood pressure, and lipids are only achieved in 50–70% of patients, including in research studies, and that individually tailored goals are needed [157].

Furthermore, our results in Paper III indicated that a microvascular focus on the patients with type 2 diabetes seemed to remain. This could also contribute to insufficient CHD prevention in clinical practice. The interpretation of secondary preventive measures after ECG screening must be done carefully since the numbers are small. However, abnormal ECG findings in patients without a clinical CHD diagnosis seemed to make little or no difference for CHD prevention with lipid-lowering medication and ASA. This occurred in spite of evidence of the predictive value of ECG abnormalities for CHD and CVD mortality [181, 182, 183, 184]. Our findings could be interpreted as a lack of appropriate focus on CHD in type 2 diabetes.

Smoking is a major risk factor for vascular complications in diabetic patients and smoking cessation has been recommended in guidelines from different countries [20, 131, 136]. Our results, however, indicate that smoking cessation has not been successful in diabetes care. Among the diabetic patients in the VIP there was no trend of reduced prevalence of smoking between time periods 1995–1999 and 2000–2004, while smoking declined in non-diabetic women (Paper I). These results were confirmed in our study in the NDR, showing no trend of reduced prevalence of smoking from 2003 to 2008 (Paper IV). The prevalence of daily smoking in 2008 among the diabetic patients in our study after three years diabetes duration was 19.2%, 95% CI 18.0–20.5 (Paper IV), which was higher than in the general population of the same age in Sweden in the same year where 15.7%, 95% CI 14.6–16.8, were daily smokers. Both men and women with diabetes smoked to a greater extent than men and women in the general population in 2008: 18.6%, 95% CI 17.8–19.4, vs. 13.6%, 95% CI 12.0–15.1, and 19.9%, 95% CI 19.0–20.8, vs. 17.7%, 95% CI 16.0–19.3, respectively [185].

**Clinical utility**

This thesis focuses on the prevention of CVD in patients with type 2 diabetes – an almost daily task of primary health care providers. Our results in Paper IV that show recent results from CVD and CHD prevention in patients with type 2 diabetes and with short duration of the disease are useful in the further
development of clinical practice. Hyperlipidaemia is least intensively treated and treatment could be substantially improved. Blood pressure targets are currently under revision, but we have shown that a substantial proportion of newly diagnosed patients with type 2 diabetes are still above the more conservative target. Since the European targets for total and LDL cholesterol from 2003 will be included in the new Swedish national guidelines expected to be published in January 2010, our findings in Paper IV indicated that, if the remaining CHD risk should be reduced, lipid levels along with blood pressure must be treated more intensively. Our findings also call for efforts aimed at smoking cessation among diabetes patients.

However, this thesis also underpins that CVD prevention has improved since the 1990s and also from 2003 to 2008. The further improvements in treatment of CVD risk factors in the subgroup with repeated reports in the NDR indicate that participation in a diabetes register could improve intervention and treatment. Our findings support using NDR participation as a quality indicator in diabetes care in Sweden.

Our findings in Paper II showed that important problems in treatment practice for diabetic patients remain to be addressed. The need for organisations to have a process for implementing prioritised clinical topics and guidelines has been described and the results of our study could be included in such a process [186]. As primary care clinicians usually work with “knowledge in practice” rather than with written sources as guidelines, new knowledge needs to be introduced through trusted sources as colleagues and other local networking [187]. Our findings also indicate a need to refocus the interaction and communication between physician and patient in order to improve the outcome of diabetes care. Problems in risk communication as well as risk management might have an even greater impact on the outcome in a situation where screening leads to a greater proportion of the diabetic patients having elevated levels of CVD risk markers but no symptoms of their disease, as revealed in our study. Improving physicians’ communication skills and the use of mutual agreement on shared decisions have also been proposed as means to improve the results of diabetes care and our findings strongly support this conclusion [160]. Our study has shown that a group setting allows GPs to discuss their dilemmas concerning their own professional role in relation to the patient and how to communicate with the diabetic patient. To consider these dilemmas in educational efforts is probably essential to achieve improved diabetes care and guideline adherence.

The usefulness of ECG as a screening tool for CHD risk is not clear. Focus on diabetic patients with the highest risk of CHD is called for. Our findings in Paper III also indicate that screening for retinopathy is well established, while there is need of quality improvements in screening for nephropathy and neuropathy.
Future perspectives

Future research aimed at improved effectiveness of evidence-based CVD prevention in people with type 2 diabetes could incorporate our findings. To find methods that improve the treatment of hyperlipidaemia and elevated blood pressure, achieve smoking cessation, and improve the communication between doctor and patient could have an impact on CHD outcome in type 2 diabetes.

If our findings in Paper IV of improved risk factor levels and of lowered estimated CHD risk in patients with short diabetes duration improves CHD outcome in real life remains to be shown.

Our findings in Paper III raises the question of the clinical usefulness of screening for CHD with ECG and if our observed insufficient awareness of CHD risk might affect the prevention of the disease.

Life style changes have not been studied in this thesis, but are important. Dietary changes and increased physical activity could have influenced the results in papers I and IV and are generally advocated. Lifestyle issues, often addressed within self-management programs, are incorporated in most national guidelines for diabetes care and several meta-analyses have demonstrated that 0.3–0.8% improvements in HbA1c, modest (1.5 kg) weight reduction, increased voluntary physical activity, and decreased medication use can be achieved in patients with type 2 diabetes through lifestyle intervention [188, 189, 190, 191]. If early pharmaceutical treatment could negatively influence desirable lifestyle changes, as discussed by the GPs in our focus group study, is not known and it may be interesting to clarify this issue.

Whether the improvements in the prevention of CVD risk demonstrated in this thesis involved improvements in patients’ quality of life or were acknowledged by patients is not known. Patient perspectives are important and should be included in future studies of quality of care. A questionnaire evaluating patients’ experiences of quality of care and health-related quality of life has been developed with the purpose of being included in the NDR reports [192]. This is in line with the need of including measures of health behaviours, patient-centred care and quality of life in the evaluation of standards of care that has been pointed out [193]. Including patient perspectives in the evaluation of the outcome of diabetes care could also help in individualising evidence-based treatment, which was a problem for the GPs in our focus group study in Paper II. Patients’ experiences of intensive CVD risk factor treatment and impact on quality of life has not been extensively studied.
CONCLUSIONS

- The introduction of treatment goals for dyslipidaemia in Swedish national guidelines in 1999 were reflected in lowered cholesterol levels in people with type 2 diabetes.

- Since the introduction of the guidelines, an increasing number of patients with type 2 diabetes were treated in accordance with guidelines.

- A remaining microvascular focus on the patients together with the revealed dilemmas within GP consultations with diabetic patients might negatively influence the remaining high incidence of CHD in the type 2 diabetes population.

- Lipid levels, blood pressure, and smoking are targets for further improvements.
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