The Epidemiology of Macrovascular Complications of Diabetes in Finland 1992-2002

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ABBREVIATIONS

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
BMI	body mass index
BP	blood pressure
CF	case fatality
CHD	coronary heart disease
CI	confidence interval
CV	cardiovascular
CVD	cardiovascular disease
CVDR	Cardiovascular Disease Register
DCCT	Diabetes Control and Complications Trial
DM	diabetes mellitus, diabetes
HbA1c	glycosylated haemoglobin
HDR	Hospital Discharge Register
HLA	human leukocyte antigen
HR	hazard ratio
ICD	International Classification of Diseases
ID	identification code
LADA	latent autoimmune diabetes in adults
LDL-C	low-density lipoprotein cholesterol
LEA	lower-extremity amputation
Major LEA	amputation at or proximal to the ankle joint
Minor LEA	amputation distal to the ankle joint
MODY	maturity-onset diabetes in the young
MONICA	Multinational Monitoring of Trends and Determinants of Cardiovascular Disease
N	number of persons observed
NHANES	National Health and Nutrition Examination Survey
OR	odds ratio
PAD	peripheral arterial disease
PAF	population-attributable fraction
PAR	population-attributable risk
RR	relative risk, risk ratio
T1DM	type 1 diabetes
T2DM	type 2 diabetes
THL	National Institute for Health and Welfare
TIA	transient ischaemic attack
U.S.	United States of America
UKPDS	United Kingdom Prospective Diabetes Study
VADT	Veterans Administration Diabetes Trial
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original publications. They are referred in the text with Roman numerals I-IV.

I   Winell K, Pääkkönen, R Pietilä A, Niemi M, Reunanen A, Salomaa V. Case fatality rates after first acute coronary syndrome in persons treated for type 2 diabetes show an improving trend**.** Diabetologia 2010;53:472-480.

II   Winell K, Pääkkönen R, Pietilä A, Reunanen A, Niemi M, Salomaa V. Prognosis of ischaemic stroke is improving similarly in patients with type 2 diabetes as in nondiabetic patients in Finland. Int J of Stroke 2011;6:295-301.

III Winell K, Niemi M, Lepäntalo M. The national hospital discharge register data on lower limb amputations. Eur J Vasc Endovasc Surg. 2006;32:66-70.

IV   Winell K, Pietilä A, Niemi M, Reunanen A, Salomaa V. Trends in population attributable fraction of acute coronary syndrome and ischaemic stroke due to diabetes in Finland. Diabetologia 2011;54:2789-2794.

1. ABSTRACT

The prevalence of diabetes is increasing rapidly in Finland. The increase is mainly due to a sedentary lifestyle and obesity, but other unknown factors most certainly also play a role, especially in diabetes of children and young adults. Diabetes is a strong risk factor for macrovascular complications. Since the incidences of acute coronary syndrome (ACS), stroke and major amputations are decreasing in Finland, it is important that diabetic patients benefit from these favourable developments as well as does the general population.

To study the development, we analysed the trends in case fatality (CF) of the first ACS and first ischaemic stroke, the incidence of lower-extremity amputations and population attributable-fractions (PAFs) of ACS and ischaemic stroke due to diabetes.

We executed a register study combining information from the national reimbursement registers of medicines, Hospital Discharge Register and Causes-of-Death Register to identify all persons that have been treated with hypoglycaemic medication or registered with a diabetes diagnosis, and their macrovascular complications from 1992 to 2002. Comparisons were made in both genders and various age groups in the nondiabetic population. Data for comparison were available through the National Cardiovascular Disease Register.

Our main findings were that the diabetic population has benefited from the favourable development to the same extent as the nondiabetic population (I, II). Prognoses after the first ACS and the first ischaemic stroke are improving. The incidence of lower-extremity amputation is decreasing (III). The prognoses of patients with diabetes are still, however, far from the prognoses of the nondiabetic population. Patients with type 2 diabetes (T2DM) had a total 1-year CF of 65.2% compared with 56.5% among nondiabetic men after their first ACS (I). The corresponding figures for women were 61.0% and 48.3%. The risk ratio (RR) for 28-day CF after the first ACS was 1.34 (95% CI (confidence interval) 1.24–1.45) among T2DM men 35–64 years of age compared with nondiabetic men in the same age group, and 1.69 (95% CI 1.44–1.97) among T2DM women with nondiabetic women, again in the same age group. The difference was greatest in the younger age groups and became less clear in the older age groups. The risk of fatal outcome within a year for 28-day survivors was considerable in patients with T2DM, RR 2.87 (95% CI 2.19–3.75) among men and 5.84 (3.70–9.23) among women 35–64 years of age. There was a statistically significant downward trend in 28-day CF and in 1-year CF of 28-day survivors both among patients with T2DM and nondiabetic patients. The trends did not differ between patients with T2DM and nondiabetic persons.

The total 1-year cardiovascular disease (CVD) CF after the first ischaemic stroke was 1.2–1.6 times higher among patients with T2DM compared with nondiabetic persons, depending on gender and age group (II). The 28-day CF was 1.1–1.3 times higher among patients with T2DM. The difference was biggest in the younger age group of men. The 1-year CVD CF of 28-day survivors was 1.4–2.2 times higher in patients with T2DM and this difference was biggest in the younger age group of women. There was a statistically significant downward trend

during the study period in CF of the first ischaemic stroke at 0–27 days and 28–364 days after the stroke. The trends did not differ between patients with T2DM and nondiabetic persons.

The crude rate of first amputations decreased from 924 to 387 per 100 000 diabetic persons (III). The decrease was similar in men and women. There were major differences in the pace of development among the hospital districts. The ratio of minor and major amputations had a positive development during the study period and the rate of first major amputations among diabetic patients decreased in the Finnish population.

The PAF of the first CVD event due to diabetes showed an upward trend among men from 11.4% (95% CI 10.8–12.0%) to 13.8% (95% CI 13.2–14.5%), p for trend < 0.0001, and a downward trend among women from 20.1% (95% CI 19.2–21.0%) to 16.9% (95% CI 15.9–17.8%), p for trend 0.0005 (IV). The upward trend was statistically significant in the first ACS event among men and the downward trend was statistically significant in the first ischaemic stroke in women.

In conclusion, our results showed that the contribution of diabetes to the burden of first CVD events remained considerable. However, despite the increase in prevalence of diabetes, the PAF of the first CVD event decreased in women and increased only slightly in men.

Strong actions should be taken to improve comprehensive treatment of risk factors after diagnosis of diabetes mellitus and efficiency of secondary prevention after a cardiovascular event. Special attention should be focused on better secondary prevention, because the largest difference between T2DM and nondiabetic persons was in 1-year prognosis of 28-day survivors after the first ACS or ischaemic stroke.

2. INTRODUCTION

The prevalence of diabetes mellitus (DM) is increasing rapidly in Finland. The increase from 1997 to 2007 was 65%. In all 284 832 persons were treated with medicines for DM in 2007 (1). Most of the increase concerns type 2 diabetes (T2DM), in which the increase was 77% during the same period. The yearly number of newly diagnosed diabetic patients is also increasing. The incidence of DM was 83% higher in 2007 than in 1997 (1). Some of the increase in the incidence of T2DM is explained by changes in diagnostic criteria and wide screening for early diagnosis, but the overweight, sedentary lifestyle and growing age of the population are also considered to explain the increase (2).

DM is associated with enhanced development of macrovascular complications (3), such as myocardial infarction, stroke and peripheral vascular disease. Microvascular complications, such as renal insufficiency or retinopathy causing visual impairment, are more specific for DM (4,5). Complications of DM cause both human suffering and growing healthcare costs. Type 1 diabetic patients with complications have 6-fold healthcare costs compared with those without complications (6). In T2DM healthcare costs are 4.4-fold among those with complications (6).

Cardiovascular (CV) events are decreasing in number and the prognosis after acute coronary syndrome (ACS) (7), stroke (8) and lower-extremity amputation (LEA) (9) has improved in Finland. It is not clear if persons with diabetes have benefited as much from the new and better treatments as nondiabetic persons. It is known that DM is a major health problem causing invalidity and early death (10). Good care of DM can prevent CV and other complications (11). All measures that help to improve treatment and prevent complications are of the utmost importance. This study presents information on the entire population of Finland over a long period of time. The development of complications reflects the quality of care and corrective actions should be considered if the outcome is not favourable.

Our study population consisted of all persons in Finland that were treated with medicines for DM. It is a register-based study that comprises the national registers of reimbursement for hypoglycaemic medicines, the Hospital Discharge Register (HDR) and the Causes-of-Death Register. This study aimed to evaluate whether the population with DM has benefited from treatments as much as the nondiabetic population. To answer the question, the case fatality (CF) proportions of first ACSs and ischaemic strokes were calculated and trends in 28- and 28–364-day CV CF were studied. The rates of LEAs were also studied as well as the population-attributable fraction (PAF) of ACS and ischaemic stroke due to DM. Even internationally there is very little current information on the PAF of cardiovascular diseases (CVDs) due to DM, although this information should be the basis for political decisions and setting of priorities.

3. REVIEW OF THE LITERATURE

3.1 Definition and types of diabetes mellitus

DM is a metabolic disease in which the blood glucose levels are chronically elevated. It is considered to be a group of diseases with both differing genotypes and phenotypes. The blood glucose is elevated due to the lack of insulin, insulin resistance or poor effect of insulin. The World Health Organization (WHO) defined DM in 1999 as a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both (12). The manifestation of clinical DM is a result of both lifestyle and genetic factors. In most cases, DM has a multigenic background, but there are also monogenic forms of DM (13).

The diagnosis of DM is based on plasma glucose level. The definition of DM has changed through the years. The current diagnostic criteria include: after fasting (at least 8 hours) plasma glucose ≥ 7.0 mmol/l; HbA1c (glycosylated haemoglobin) ≥ 6.5% (using the standardized Diabetes Control and Complications Trial (DCCT) assay); 2-hour plasma glucose ≥ 11.1 mmol/l in the oral glucose tolerance test using a 75-g glucose load or random plasma glucose ≥ 11.1 mmol/l in a person with diabetic symptoms (14). The test should be repeated if the patient does not have the classical symptoms of DM.

The main types of DM are type 1 diabetes (T1DM) and T2DM. In T1DM insulin production in the pancreas diminishes, due to an autoimmune process that destroys the insulin-producing beta-cells. The disease usually starts in childhood or the teenage years. Persons with T1DM require insulin for survival. A similar autoimmune process can also start later in life, often after the age of 35, resulting in insulin deficiency. This type of diabetes is called LADA (latent autoimmune diabetes in adults). It resembles T2DM in the slow development of the disease. T2DM usually starts in adulthood, with increasing incidence by age. In the LADA type of DM the insulin production diminishes more rapidly than in T2DM.

T2DM is characterized by changes in insulin secretion and action. Resistance to insulin causes not only hyperglycaemia, but also other harmful metabolic changes. Patients are often overweight in T2DM (15). MODY (maturity-onset diabetes in the young) is a group of DM types caused by monogenic disturbances with insufficient insulin response to glucose (16). Typically, the disease is detected in adolescence or young adulthood. It does not have the same kind of destructive autoimmune process of the pancreas as T1DM. Another strongly hereditary DM type is mitochondrial DM with deafness (17).

Temporary elevation of blood glucose can be seen in acute illnesses or stress. This is also the case with gestational DM during pregnancy (18). Sometimes even neonatal DM can disappear (19).

3.2 Pathogenesis and risk factors of diabetes

In T1DM the autoimmune process destroys the beta-cells of the pancreas. This results in a total or nearly total deficit of insulin. The initiation of the disease is considered to be the result of environmental influence on genetically predisposed persons (20).

In T2DM patients often have hyperinsulinaemia, insulin resistance and disturbed beta-cell functioning (21). The pathogenesis of T2DM is not known, but the lack of exercise, excessive energy intake and reduced energy consumption seem to play roles (2). In the U.S. (the United States of America) it was estimated that the lifetime DM risk at 18 years of age increased from 7.6% to 70.3% between underweight and very obese men (22). Among women the increase was from 12.2% to 74.4% (22). In addition, dysfunctional adipose tissue in obesity (23) and an impaired incretin system (24) have been claimed to play roles in causing T2DM. Since mitochondria are central to fuel consumption and energy production, it is also believed that mitochondrial dysfunction plays a role in the pathogenesis of T2DM (25). The risk for T2DM can be predicted fairly accurately by simple measurements and health habit information (26).

T1DM has a strong genetic basis. Human leukocyte antigen (HLA) genes play a major role, but several non-HLA candidate genes have been detected as well (27). Some people have a genetic predisposition to acquire T2DM. The aetiology of T2DM is polygenic and the clinical expression often requires a sedentary lifestyle (28). The increasing number of predisposing risk genes increases the risk of disease. MODY-type DM is caused by a single gene defect and can therefore be determined by DNA (deoxyribonucleic acid) analysis (16). Neonatal DM is also caused by a single gene defect (19).

3.3 Prevalence and incidence of diabetes

The prevalence of DM has increased rapidly in Finland. The prevalence of persons treated with hypoglycaemic medication doubled from 1988 to 2002 (Fig. 1) (29). The rapid increase in prevalence has also continued after 2002. The number of diabetic patients increased by 65% from 1997 to 2007 (1). A total of 284 832 persons were treated with hypoglycaemic medication in 2007. Most of the increase has been due to T2DM in which the increase in prevalence was 77% from 1997 to 2007 (1).

The increasing prevalence of DM is a worldwide phenomenon (30,31). Its development in the U.S. has been similar to that in Finland (32). In China, the prevalence of DM was 10.6% in adult men and 8.8% in adult women in 2007 (33). The prevalence has increased together with the changes in population characteristics: increasing age, body mass index (BMI) and people living under urban conditions (33). The world prevalence of DM among adults (20–79 years of age) was estimated to be 7.7% by the year 2030, including a 69% increase in the numbers of adults with DM in the developing countries and a 20% increase in the developed countries from 2010 to 2030 (31).

Figure 1. Prevalence of diabetes during 1988–2002 in Finland (29).
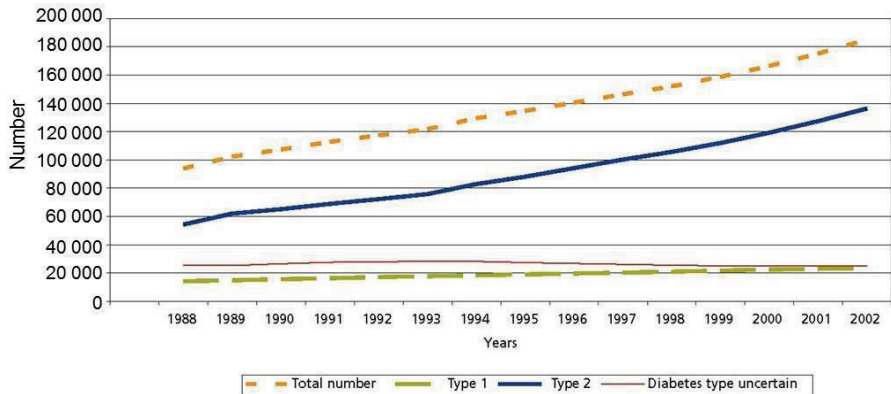
The number of newly diagnosed diabetic patients has also increased constantly in Finland (1). The increase in incidence of DM concerns both T1DM and T2DM. The incidence of DM was 83% higher in 2007 than in 1997 (1). This development resembles again the development reported from the U.S. (Fig. 2) (32).

Some of the worldwide increase can be explained by the new definition of DM given in 1999, when the diagnostic plasma glucose level was lowered to 7.0 mmol/l from the previous 7.8 mmol/l (12). The screening, diagnostic and treatment activities of DM have also increased (34,35) after the harmful effects of hyperglycaemia were shown convincingly (3,4). Studies from several countries have shown that many people are unaware of their DM (36–38). As late as in 2007, a population survey in Finland showed that two thirds of diabetic persons did not know about their illness (39).

The reasons for the increase in incidence of T1DM are still unknown. Environmental factors and/or childhood diet are believed to play a major role (40).

Gestational DM is a risk factor for the future development of T2DM (41). In a meta-analysis, women who had gestational DM had 7.43 (95% confidence interval (CI) 4.79-11.51) -fold risk for developing T2DM compared with those without gestational DM (41). The risk for a mother and also for her child of acquiring DM after gestational DM was predicted by the mother's high BMI 15 years after the delivery (42).

T2DM can be prevented or at least postponed with lifestyle interventions targeted to weight reduction by physical exercise and changes in eating habits (43). Increase in leisure time physical activity can prevent DM (44). Lifestyle interventions seem to have a long-lasting influence in preventing DM (45), with a delay in the onset of DM in high-risk adults (number needed to treat (NNT) 6.4) (46).

Figure 2. Incidence of newly diagnosed diabetes in the U.S. during 1980–2007 and projected future scenarios, including 95% confidence intervals (CI) (32) (Open access material, free for use).
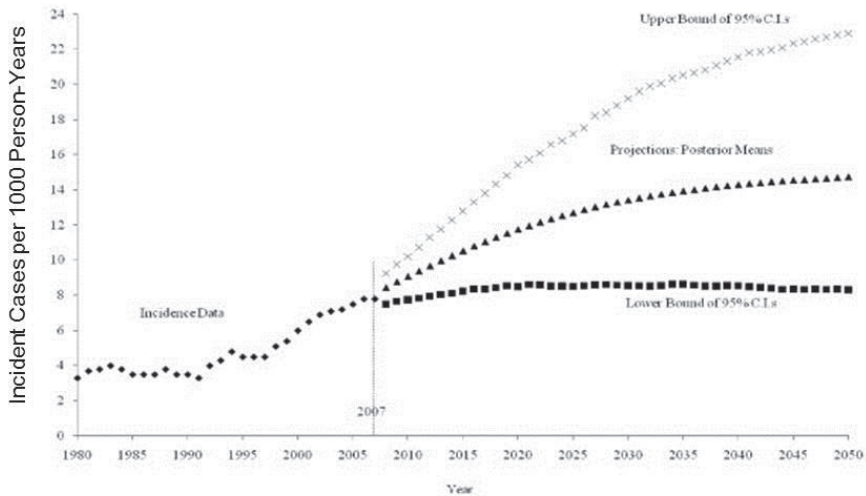
3.4 Complications of diabetes

The vascular complications of DM are divided in micro- and macrovascular complications. Microvascular complications include nephropathy, neuropathy and retinopathy. Microvascular complications are strongly related to the level of hyperglycaemia (4,5). Macrovascular complications include coronary artery disease, cerebrovascular disease and peripheral arterial disease (PAD). The effect of blood glucose level on macrovascular complications is not clear in T2DM (47).

DM also increases the risk of several other diseases, such as liver disease, infections, mental disorders, self-harm, chronic obstructive pulmonary disease and cancer (48–53). The risk of cancer death is increased in liver, colon and breast cancers in both genders (54). Among diabetic women, the risk of cancer death is increased in endometrium cancer and among diabetic men in oral cavity, pharynx and bladder cancers (54).

In general, DM reduces the life expectancy of a 50-year-old person by about 6 years, and about 40% of the difference in survival compared with nondiabetic persons is due to excess in nonvascular deaths (53). A 1.80 (95% CI 1.71–1.90) hazard ratio (HR) was shown among persons with DM in comparison to those without DM for all-cause mortality and 2.32 (95% CI 2.11–2.56) for CV mortality (53). In England and Wales the additional mortality among persons with DM was estimated to be 39.8% (10).

3.4.1 Complications in type 1 diabetes

Patients with T1DM develop both micro- and macrovascular complications. After 30 years of conventional therapy (insulin once or twice per day), 50% had proliferative retinopathy, 25% had nephropathy and 14% CVD. In the intensive treatment group, the figures were 21%, 9% and 9%, respectively (55). Development of nephropathy doubles the risk for CV death (56).

The DCCT, which tested the effect of intensive glucose treatment in patients with T1DM, showed a risk reduction in microvascular complications (5). The Epidemiology of Diabetes Interventions and Complications (EDIC) study, an observational follow-up of the DCCT study T1DM cohort, showed a decrease by 42% (95% CI 9–63%, p = 0.02) in the intensive glucose treatment group in CV complications (57). The intensive intervention also resulted in 63% reduction in retinopathy progression, 47% decrease in the development of severe nonproliferative diabetic retinopathy, 39% and 54% reductions in microalbuminuria and macroalbuminuria, respectively, and 60% reduction in clinical neuropathy at 5 years from the beginning of study (57). Aggressive early intervention before the manifestation of complications yielded the best results. In both the intensive and conventional treatment groups in the DCCT, there was approximately a 40% reduction in the risk of retinopathy progression for each 10% proportional reduction in HbA1c (58).

The initial treatment of risk factors at the beginning of the disease plays an important role in the development of CV complications (59). An additional 10-year follow-up of DCCT patients after completion of the randomized trial showed a legacy effect that resulted in hazard reductions of 53–56% (p < 0.001) in the progress of diabetic retinopathy (60). The development of retinopathy was almost totally explained by reduction in the mean HbA1c level (61). The beneficial effect of intensive glucose treatment also proved to protect against hypertension and nephropathy 7–8 years after the initial trial (62). Prior intensive treatment was protective even for arterial calcification (HR 0.72 (95% CI 0.55–0.94)), but not for occlusion measured by the ankle-to-brachial ratio index (ABI) (63, 64).

3.4.2 Complications in type 2 diabetes

T2DM is associated with CV complications, such as coronary heart disease (CHD), stroke and limb ischaemia, but also with microvascular complications, such as nephropathy (65,66), neuropathy (67) and retinopathy (68). Liver dysfunction is one of the comorbidities in T2DM (69). In addition, obstructive sleep apnoea is also a comorbidity in T2DM (70). Hypertension is common among newly diagnosed T2DM patients. At 2 and 9 months after the diagnosis of DM, 35% of the males and 46% of the females were hypertensive (mean blood pressure (BP) ≥ 160 mmHg systolic and/or ≥ 90 mmHg diastolic) (71). Patients with both hypertension and DM have approximately four times the CV risk of nondiabetic nonhypertensive subjects (72).

T2DM increases the risk for CHD (73,74). It was estimated, based on the Framingham study, that after adjustment for age, sex and CHD risk factors, the risk of CHD was 1.38 times higher

for each 10-year increase in duration of DM (95% CI 0.99–1.92), and the risk for CHD death was 1.86 times higher (95% CI 1.17–2.93) for the same increase in duration of DM (75). The Euro Heart Survey suggested that actually the majority of patients with acute manifestations of coronary disease have either DM or abnormal glucose regulation (76). Stroke is also more common in persons with T2DM than in nondiabetic persons: 1.5–5 times more common in men and 2–8 times more common in women (77–79). Of about 600 T2DM patients 60 years of age or older in the Netherlands, 27.7% (95% CI 24.1–31.4%) had previously unknown heart failure (80).

A cross-sectional study from Spain, in which a random sample of 2642 T2DM patients treated in primary care during 2007 was examined, showed a 34.1% prevalence of kidney disease measured by lowered glomerular filtration rate (66). In France, the prevalence of chronic kidney disease among 8926 T2DM patients, mean age 66 years, was 29% in 2007 (81). In India, a study of 1414 newly diagnosed T2DM patients revealed a 4.8% prevalence of diabetic retinopathy and 10.5% prevalence of both diabetic nephropathy and neuropathy (82).

3.5 Macrovascular complications in diabetes

3.5.1 Epidemiology, risk factors and prevention of macrovascular disease in persons with diabetes

The risk of CVD in men with DM is 3-fold and in women with DM 5-fold in comparison to those without diabetes (11). DM accounts for 56% of all CVD events in men and 78% in women (3). Most CVD deaths occur in those with DM (3). Several risk factors contribute to the development of CVDs in DM, e.g. high blood glucose, dyslipidaemia, high BP, microalbuminuria, obesity, male gender and age. Active treatment of multiple risk factors in T2DM is apparently beneficial (83–85). Low socioeconomic status, depression, stress and anxiety increase CVD risk in all persons, including patients with DM (11).

The ADDITION-Europe study, which was a cluster-randomized trial aiming at multiple risk factor reduction in 3057 screen-detected T2DM patients, was not able to show a significant decline in CV events within 5 years (86,87).

BP treatment of patients with DM lowers the incidence of CV complications (88), and it is apparently less important which drug or combination of drugs is used (89). Sowers et al. estimated in their review article that 75% of CVD is explained by high BP in patients with DM (90).

The United Kingdom Prospective Diabetes Study (UKPDS) showed that the higher a patient's blood glucose level, the higher is the risk of dying of ACS or stroke in T2DM (91). A percentage point decrease in HbA1c decreased DM-related mortality by 21%, myocardial infarctions by 14% and microvascular complications by 37% (92).

On the other hand, several other studies were unable to show reduction in CV complications after intensive glucose control in T2DM (93–96). The Action to Control Cardiovascular Risk in

Diabetes (ACCORD) study showed no benefit from intensive treatment compared with standard therapy. CVDs, a composite of CVD death, nonfatal myocardial infarction and nonfatal stroke, were not reduced with the intensive treatment strategies (97). However, the total mortality increased, when the treatment goal for HbA1c was < 6.0% compared with the standard therapy goal of 7.0–7.9% (95,98). The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial was likewise unable to show any statistically significant differences in CVD event rates or CVD deaths among patients with disturbed glucose tolerance (99). A recent meta-analysis comprised of 13 randomized trials on intensive glucose control in T2DM suggested no significant changes in total mortality or CV mortality, but showed a reduction in nonfatal myocardial infarctions, risk ratio (RR) 0.85 (95% CI 0.74–0.96, p < 0.001) (100). Another meta-analysis examining the benefit of intensive glucose control in T2DM showed a 17% reduction in nonfatal myocardial infarction events, odds ratio (OR) 0.83 (95% CI 0.75–0.93) and a 15% reduction in CHD events, OR 0.85 (95% CI 0.77–0.93) in the intensive care group, but no change in stroke events or all-cause mortality (101). The results were unexpected, because poor glycaemic control had in previous studies suggested an increase in CV events (91,92). Subgroup analyses of these large trials have provided evidence that patient characteristics, such as age, DM duration and tendency to hypoglycaemia are important (102). The differences between the results of the UKPDS study (91) and ACCORD (97), Action in Diabetes and Vascular Disease - PreterAx and DiamicroN MR Controlled Evaluation (ADVANCE) (94) and Veterans Administration Diabetes Trial (VADT) (93) study results have been explained by the fact that the UKPDS recruited newly diagnosed T2DM patients, while the other studies also included patients with a long DM history (103). The influence of duration of DM was shown in the VADT study, which targeted difficult-to-control diabetic patients (104).

A meta-analysis showed an overall RR of 1.26 (95% CI 1.16–1.36) for LEA for every percentage point increase in the HbA1c level (105). This meta-analysis did not distinguish T1DM from T2DM.

Dyslipidaemia, e.g. elevated triglycerides, low levels of high-density lipoprotein cholesterol and high levels of low-density lipoprotein cholesterol (LDL-C), is a risk factor for macrovascular diabetic complications (106,107). Lowering LDL-C with diet or lipid-lowering medication has been an important aim in reducing the CV risk of patients with DM. Statins reduce all-cause mortality by 9% and major vascular events by 21% for every mmol/l -unit decrease in LDL-C (108). Data from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study and ACCORD Lipid study suggest that fenofibrate reduces CV complications only slightly (109–111).

Microalbuminuria strongly predicts CV morbidity and mortality in individuals with DM (112). In a cohort study, the risk for CHD or stroke was doubled in those with microalbuminuria in comparison to those without (113).

Obesity increases the risk of CHD through insulin resistance, DM, arterial hypertension and dyslipidaemia (114). Insulin resistance and the compensatory hyperinsulinaemia are predictors of CHD (115). Insulin sensitivity improves with weight loss (116). Weight reduction improves lipid profiles and inflammation (117), which leads to a decrease in CV risk.

Bariatric surgery is used in obese T2DM patients to reduce CV risk factors and incidence of T2DM (118). It also reduced CV deaths in obese Swedish patients, HR 0.47 (95% CI 0.29–0.76) and first-time CV events, adjusted HR 0.67 (95% CI 0.54–0.83) (119). Bariatric surgery resulted in better glycaemic control than conventional therapy in severely obese T2DM patients (120). Apparently, even the occurrence of retinopathy decreases after bariatric surgery (121). This improvement could not be explained by improvement in glycaemic control only (121). The mechanism by which bariatric surgery promotes rapid improvement in systemic metabolism and long-term weight loss remains incompletely understood (122). A 6-year follow-up comparing treatment of extremely obese patients with conventional therapy and bariatric surgery showed higher rates of DM remission and lower risk of CV events measured by changes in risk factors (123). The long-term effects of bariatric surgery in preventing CVD remain to be seen.

Recent studies have examined the predictive roles of novel risk factors in development of CVD. The novel measures that have been studied include C-reactive protein, lipoprotein-associated phospholipase A, genetic markers and markers of subclinical organ damage, for which there are varying levels of evidence (2, 124). There is some evidence that oxidative stress markers play a role in CVD development (125). Oxidized-LDL-C, myeloperoxidase, nitrotyrosine and lipid peroxidation measures are used as such markers. Biomarkers from genomics, transcriptomics, proteomics and metabolomics have also been examined (126). Mildly elevated serum bilirubin levels seem to have a protective effect against CVD and also DM (127).

Genetic control influences CHD morbidity directly and also via control of the various risk factors (128,129).

The above list of recent literature shows, more than 20 years after we began collecting our research data, that there are still controversies over the real benefit of treating different risk factors. During the study years and also before the appearance of diabetic complications, knowledge of the causes of these complications has affected the treatment regimens in many ways.

3.5.2 Epidemiology, risk factors and prevention of acute coronary syndrome

DM is a severe risk factor for CHD death, increasing the risk among men to 2–3-fold and among women to 3–6-fold (74, 130). The large, cross-sectional INTERHEART study in 52 countries estimated that 9.9% of myocardial infarctions were due to DM (131). Hypertension triples the CHD risk among patients with T2DM (132). A study in Sweden showed that DM is the strongest risk factor for recurrent myocardial infarction (133).

In Ontario, Canada the rate of patients admitted to hospital for acute myocardial infarction fell from 1992 to 2000 to a greater extent in the diabetic than in the nondiabetic population (-15.1% vs. -9.1%, p < 0.0001), but because at the same time the number of persons with DM

increased from 405 471 to 670 602, the number of coronary events among persons with DM increased by 44.6% and ACS deaths by 17.2% (134).

The National Health and Nutrition Examination Survey (NHANES) I (from 1971 to 1975) and the Epidemiologic Follow-up Survey (from 1982 to 1984) followed the cohorts for 8–9 years and showed a 16.6% decrease in ischaemic heart disease mortality between the cohorts among men with DM, while the decrease was 43.8% for nondiabetic men. Women with DM showed a 10.7% increase during the same period, while nondiabetic women showed a 20.4% decrease in ischaemic heart disease mortality. The change was significant for nondiabetic men, but not for men with DM or women (135).

Many reports have emphasized the disproportionately increased risk of coronary disease that DM brings about in women (136,137). The Framingham study showed that the presence of DM doubled the risk for recurrent infarction in women but not in men after the first ACS event (138). The RR in men was 1.6 (95% CI 1.0–2.4) and in women 2.5 (95% CI 0.9–6.9) (138). These findings were, however, challenged in a meta-analysis of 16 studies that adjusted for classic coronary risk factors (age, hypertension, total cholesterol and smoking) but which found no excess RR for CHD mortality, depending on gender (74).

A cohort study examined the influence of alcohol intake in type 2 diabetic persons. Alcohol had a protective effect against CHD death at all the doses examined (139). The Nurses' Health Study showed similar benefits, both in preventing fatal and nonfatal coronary disease (140).

3.5.3 Effect of diabetes on case fatality of acute coronary syndrome

The elevated risk of CHD death in individuals with DM can be due either to increased incidence of ACS events, or increased CF, or both. The WHO project Multinational Monitoring Trends and Determinants of Cardiovascular Disease (MONICA) highlighted the situation in several countries. The CF of the first ACS was compared in three countries from the late 1980s to the mid-1990s (Table 1). In Australia the RR of fatal outcome at 28 days after the onset of first ACS among the 5322 patients in hospital care was 1.56 (95% CI 1.19–2.04) among women with DM and 1.25 (95% CI 1.02–1.53) among men with DM compared to their nondiabetic counterparts (141).

A corresponding study in Finland that examined 4065 first ACS patients 25–64 years of age revealed an RR of 2.60 (95% CI 1.71–3.95) for death within 28 days among women with DM and 1.58 (95% CI 1.15–2.18) among men with DM (142). The RR of prehospital death was 0.95 (95% CI 0.58–1.54) among women with DM and 1.25 (95% CI 1.03–1.52) among men with DM. The RR of 1-year fatality of 28-day survivors was 4.17 (95% CI 2.05–8.51) among women with DM and 1.97 (95% CI 1.25–3.12) among men with DM. In that study, the total 1-year excess risk for death after the first ACS was 1.86 (95% CI 1.40–2.46) for women with DM and 1.38 (95% CI 1.18–1.61) for men with DM.

Table 1. Short- and long-term case fatality (CF) after the first acute coronary syndrome. Comparison of studies in three countries, (N = number of persons observed).

Study and study years	Country	Persons with diabetes (N) (age range)	Out-of-hospital CF men/women	CF at days 1–28 men/women	CF at 1 year men/women	Comment
Chun B et al., 1985–1994 (141)	Australia	557 (age 30–69 years)	Not available	25%/25%	Not available	Hospitalized patients only, CF is age-adjusted
Miettinen H et al., 1988–1992 (142)	Finland	620 (age 25–64 years)	28.3%/10.4%	14.4%/21.7%	44.2%/36.9% (15.9%/25.9%, if excluding pre-hospital deaths)	1-year CF includes pre-hospital deaths, CF is age- and area-adjusted
Koek H et al., 1995 (143)	The Netherlands	2018 (all ages)	Not available	18%/22%	29.8%/26.9%	Hospitalized patients only, CF is crude rate

In the mid-1990s a nationwide register study in the Netherlands followed up persons with their first ACS (143). After multivariate adjustment, the 28-day RRs became nonsignificant. The RR for women with DM was 1.12 (95% CI 0.97–1.28) and for men with DM 1.16 (95% CI 0.99–1.36). The corresponding 1-year multivariate-adjusted RR for women with DM was 1.33 (95% CI 1.17–1.50) and 1.23 (95% CI 1.09–1.37) for men with DM.

A population-based registry study from northern Sweden followed the time trends in ACS CF in the age group 35–64 years from 1989 to 2000 among both populations with and without DM (144). The 28-day CF decreased significantly in both nondiabetic men and women, but not in men and women with DM. The 1-year mortality rate also declined significantly among nondiabetic men and women but not among men and women with DM. However, there was a downward trend among women with DM in both 28-day and 1-year CF (144).

A community-based study from Massachusetts in the U.S. examined the 1-year CF after an ACS among persons with diabetes during 1975–1999. The CF rates were higher for women than for men, 21.3% vs. 14.9%. The 1-year CF decreased from 39.2% to 17.5% among women with DM and from 18.9% to 9.5% among men with DM (145).

3.5.4 Epidemiology, risk factors and prevention of ischaemic stroke

The overall incidence of stroke has decreased in Finland, while the prognosis after stroke has improved during the period 1991–2002 (8). The age-standardized incidence of first-ever stroke decreased annually by 2.2% (95% CI 1.9–2.4%) among men and 2.5% (95% CI 2.2–2.8%) among women 35–74 years of age. In patients 75–84 years of age, the decrease was 2.6% per year (95% CI 2.2–3.0%) among men and 3.2% per year (95% CI 2.9–3.5%) among women (8). In the age group 35–74 years, the 28-day CF of first-ever stroke decreased annually by 3.2% (95% CI 2.5–3.9%) among men and by 3.0% (95% CI 2.2–3.8%) among women (8). A study in Sweden showed that the age-standardized overall incidence of first-

ever stroke in the age group 35–65 years increased from 1989–1991 to 1998–2000 by 19% in men and 33% in women (146). Part of the increase may have been due to improved diagnostics and detection of smaller strokes. Furthermore, the study was based on the Hospital Discharge Register only and missed out-of-hospital stroke deaths, because no CVD register was in use. The out-of-hospital stroke deaths may have decreased during the study period.

Stroke risk is increased 1.5–5-fold among men and 2–8-fold among women with DM (77–79,147). The cross-sectional INTERSTROKE Study in 22 countries estimated that 5.0% of ischaemic strokes were caused by DM (148). Concomitant hypertension doubles the risk for stroke (132). In the U.S., a study investigated all admissions from Veterans Administration hospitals between 1990 and 1997 (N (number of persons observed) = 48 733) and showed that an increasing proportion of ischaemic stroke patients had DM, 31% in 1997 (149). In Canada, the rate of patients admitted to hospital for stroke fell to a greater extent in the population with DM than the population without DM, -24.2% vs. -19.4% (p < 0.0001) from 1992 to 2000, but due to the increase in the number of persons with DM in the population, the stroke events increased by 26.1% and stroke deaths by 13.2% (134).

A population-based study in Finland investigated patient prognosis after the first stroke event from 1990 to 1998 (150). The study showed, using logistic regression analysis, that DM is a predictor of disability after stroke, OR 1.51 (95% CI 1.27–1.81).

3.5.5 Effect of diabetes on case fatality of stroke

A study in Finland showed that the 28-day CF was higher in patients with DM than in those without (20.0% vs. 16.9%, p = 0.020) in the 1990s (150). A Veterans Administration hospital study between 1990 and 1997 showed no significant difference in 60-day or 1-year postdischarge mortality between the stroke patients with or without DM, but the Kaplan-Meier survival plot showed that persons with DM had shorter long-term survival (log-rank, p < 0.001) and the multivariate Cox proportional hazards regression showed that the hazard of death for patients with DM was 15% more than for nondiabetic persons after controlling for other covariates (HR = 1.15, p < 0.001) (149).

The National Acute Stroke Israeli Survey followed the first-ever acute ischaemic stroke survivors (N = 1079) starting in 2004 for 1 month and for 3 years. DM increased the HR of mortality to 1.6 (95% CI 1.0–2.4) among the 1-month survivors (151).

A population-based register study in Sweden followed 15 382 stroke patients 35–74 years of age from 1985 to 2003. The CF and mortality of stroke declined for all groups, except women with DM after the first-ever stroke during the study period. The time trends in CF and mortality did not differ significantly between patients with and without DM (79).

Among 12 686 patients with an acute ischaemic stroke in Canada, those with DM had a less favourable outcome after thrombolysis than their nondiabetic counterparts, 24.3% vs. 31.1%, RR 0.90 (95% CI 0.82–0.98) (152).

3.5.6 Epidemiology, risk factors and prevention of lower-extremity amputation

The global variation in the incidence of all forms of LEA ranges from 46.1 to 9600 per 100 000 and of major (at or proximal to the ankle joint) amputation from 5.6 to 600 per 100 000 in the population with DM (153). The risk for LEA was over 20 times higher among patients with DM than in nondiabetic patients in the entire population of England (154). The risk for LEA was 8-fold among men and 6-fold among women with DM compared with nondiabetic persons in Germany (155). In Finland, a 7-fold risk was shown for a major amputation among persons with DM compared with nondiabetic persons (156).

A study in England found no significant change in 1-year mortality after an amputation among diabetic persons from 2000 to 2004 (157). The study also showed a reduction in amputations among T1DM patients, but an increase among T2DM patients of from 2.0 to 2.7 per population of 100 000 (157). A similar trend was shown from the Spanish HDR during 2001–2008. In patients with T1DM, the incidence of minor (distal to the ankle joint) and major LEAs decreased significantly, from 0.88 to 0.43 per 100 000 inhabitants and from 0.59 to 0.22 per 100 000 inhabitants, respectively. In patients with T2DM, the incidence of minor LEAs increased significantly, from 9.23 to 10.9 per 100 000 inhabitants and major LEAs from 7.12 to 7.47 per 100 000 inhabitants, also significantly (158).

A nationwide follow-up of T1DM patients, who had been identified from the HDR in Sweden, demonstrated a cumulative probability of nontraumatic LEA of 11.0% for women and 20.7% for men (p log-rank < 0.01) by the age of 65 years. The RR for nontraumatic LEA was 0.6 (95% CI 0.5–0.8) during 2000–2004, compared with the period 1975–1999 (159).

The incidence of major amputations among persons with DM fell from 27.2 to 6.9 per 100 000 inhabitants in Copenhagen, Denmark in a hospital-based study from 1981 to 1995 (160). Similar development was reported from the hospital in Lund, Sweden (161). The incidence of major amputations decreased from 16 (95% CI 11–22) to 6.8 (95% CI 6.1–7.5) per 100 000 inhabitants between the first and last 4-year period from 1982 to 2001 (161). Ipswich Hospital in the U.K. reported a decrease in major amputations from 7.4 to 2.8 per 100 000 in the general population from 1995 to 2005 (162).

Smoking is a strong risk factor for PAD, but hypertension, hypercholesterolaemia and T2DM are also associated with increased risk of PAD (163).

3.5.7 Total cardiovascular burden in diabetic individuals

The Emerging Risk Factors Collaboration analysed data on over 820 900 people and found an HR of 2.32 (95% CI 2.11–2.56) for death from vascular causes among participants with DM, in comparison to those without DM, after adjustment for baseline age, sex, smoking status and BMI (53). DM exhibits approximately a 2-fold risk for most vascular complications (164).

The population-based health surveys NHANES I, II and III compared CV mortality among 35–74-year-old persons with and without DM in three cohorts which were started in 1971–1975, 1976–1980 and 1988–1994. The mortality rates were determined through 1986, 1992 and 2000 for the three surveys, respectively. The study demonstrated a decrease in CV mortality among men and women without DM. The changes were significant. There was also a decrease in CV mortality among men with DM, but this was not statistically significant. Among women with DM there was no change in CVD mortality (165). CVD has been the most common underlying cause of death in DM, accounting for 44% of deaths in T1DM and 52% of deaths in T2DM (166).

A study in England concluded that there was a 5-fold risk among persons with DM for ACS admission to hospital and a 3.5-fold risk for stroke compared with nondiabetic persons (167). The study compared vascular admission rates in 2004 and 2009. ACS decreased, with a rate ratio of 0.95 (95% CI 0.93–0.97) per year among persons with DM. The development did not differ between genders in ACS, but it did in stroke, where men with DM had a rate ratio of 1.00 per year (95% CI 0.99–1.01), but women showed a significant downward trend, rate ratio 0.99 per year (95% CI 0.97–0.99) (167).

3.5.8 Population-attributable fraction of cardiovascular diseases due to diabetes

The Framingham Heart Study estimated that the PAF of CVD due to DM increased from 5.4% (95% CI 3.8–6.9%) in the period from 1952 to 1974 to 8.7% (95% CI 5.9–11.4%) in the period 1975–1998 (168). Based on data from the NHANES II study (1976–1980), the authors estimated that DM accounts for at least 3.6% of all deaths and 5.2% of CVD deaths in U.S. adults (169).

In Malmö, Sweden a population screened from 1974 to 1992 was followed up for a maximum of 28 years. The population-attributable risk (PAR) of coronary events due to DM was estimated to be 3%, 6% for women and 2% for men (170). In Spain, the PAR of CHD due to DM was estimated to be 10.1% (95% CI 0–16.8%) (171). The latter study was based on a cohort of 6124 adults.

In Japan, the PAF of CHD due to DM was estimated to be 6.3% between 1990 and 2006 (172). In Taiwan, the PAF of total mortality due to DM was 26.8% (95% CI 8.3–48.5%) among men and 19.9% (95% CI 3.4–42.3%) among women (173).

A study in Germany, covering a population of 1.6 million people in a statutory health insurance scheme, showed a PAF for the first nontraumatic LEA of 0.59 for men and 0.40 for women due to DM during the years 2005–2007 (155). The authors expected that the St. Vincent target of 50% reduction in amputations among persons with DM could be reached in Germany, because a previous study had shown a PAF of 0.72, due to DM (174).

4. AIMS OF THE STUDY

The main aim of the study was to examine the epidemiology of macrovascular complications of DM in the nationwide diabetic population in Finland during the period 1992–2002. The specific aims were to examine secular trends in

1) the CF of the first ACS among all persons treated for T2DM in Finland,
2) the CF of the first acute ischaemic stroke among all persons treated for T2DM in Finland,
3) major LEAs, and the differences between the hospital districts in the incidence of major LEAs among the Finnish population with DM and
4) the PAF of the first ACS and ischaemic stroke in Finland.

5. MATERIAL AND METHODS

5.1 Study population

The study population comprised all persons in Finland who were treated with hypoglycaemic medicines for their diabetes (DM) during the period from 1988 to 2002. We also included patients for whom DM was listed among the diagnoses in the National HDR, irrespective of drug treatment. In all, 308 447 diabetic patients were included in the study. The setup of the study population is shown in Figure 3 (29).

Figure 3. Setup of the study population, modified with author's permission, originally published in Diabetes in Finland. Prevalence and Variation in Quality of Care (29) (THL – the National Institute for Health and Welfare, N = number of persons observed).
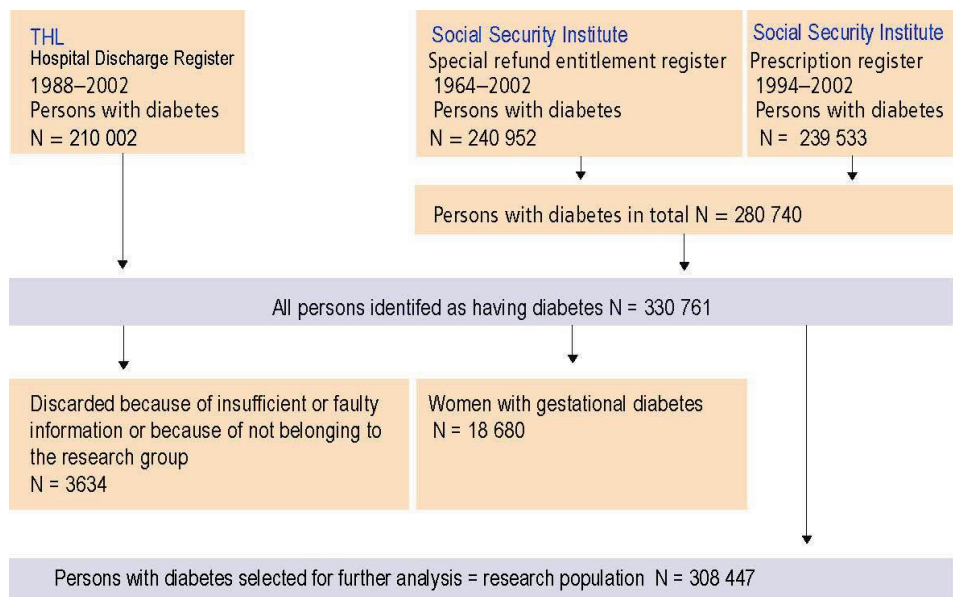
5.2 Source registers and registry linkage

The data for this study originated from four nationwide healthcare registers: two drug reimbursement registers of the National Social Insurance Institute, the National HDR of the National Research and Development Centre for Welfare and Health (Stakes), which currently is part of THL – the National Institute for Health and Welfare, and the National Causes-of-Death Register of Statistics Finland. The special reimbursement (or special refund entitlement) register of medicines includes all patients with DM in Finland who have been entitled to special reimbursement for hypoglycaemic medication during the study period. These data extend back to 1964. To receive this special reimbursement the patient needs to obtain from his/her physician a statement documenting the clinical and laboratory findings

that have led to the diagnosis of DM. The statement is reviewed by an expert physician of the Social Insurance Institute before the special reimbursement is granted. In DM the reimbursement was 100% for hypoglycaemic medicines during the study period, which is why in practice every medically treated person with DM was included in the register. The Social Insurance Institute also keeps another register that has information on patients with DM. Since 1994 there has been a prescription register on persons who received reimbursement to standard amount (about half the price during the study period). The latter register also has information on those diabetic patients that did not receive the special reimbursement.

The National HDR includes information on all hospitalizations in Finland. The diagnoses are recorded by the physician in charge of hospital care, using the International Classification of Diseases (ICD) codes. The ICD-10 classification has been used since early 1996 and the ICD-9 classification previous to that. This study has information on diabetic persons and their complications obtainable from the HDR since 1988. The National Causes-of-Death Register information of the study population was also included since 1988. The Causes-of-Death Register has information on all deaths of Finnish citizens and permanent residents. The physician in charge of treatment codes the underlying and direct cause of death, using the ICD codes. The coding is then checked and revised if necessary, by a nosologist working under the guidance of a specialist in forensic medicine in Statistics Finland. The CV diagnoses in the Finnish HDR and in the Causes-of-Death Register have been validated (175–177).

The registers listed above were linked together on an individual basis, using the personal identification code (ID) unique to every permanent resident in Finland. The personal ID includes a control part that minimizes the risk of mixing different persons in the registers. Pajunen et al. reported that "The number of erroneous personal IDs in the Finnish administrative registers is negligible and the quality of the HDR data has continually improved. In 1991, 0.26% of the personal identification codes in the HDR were incomplete; in 2002, less than 0.08% of codes had any defects. None of the personal identification codes in the Causes-of-Death Register were incomplete." (175).

After the record linkage was performed, the personal ID was replaced with an artificial study ID to create an anonymous dataset for analyses. The Ethical Committee of the National Public Health Institute approved the study.

5.3 Definitions of variables in the registers

5.3.1 Diabetes mellitus

DM was defined in the reimbursement registers by the use of hypoglycaemic medication with the ATC (the Anatomic Therapeutic Chemical classification system) code A10, and in the National HDR and in the Causes-of-Death Register with the ICD-9 codes 250 and ICD-10 codes E10–E14.

The type of DM was determined, based on the age at the time of first diagnosis and the type of treatment given. Patients who were under 30 years of age and treated with insulin only or in combination with metformin, as well as those who were between 30 and 40 years of age when treatment with insulin only was started, were considered to have T1DM. Those patients with DM who were under 30 years of age and in chronic institutional care were also considered to have T1DM if there was no knowledge of the type of medical treatment. All others were considered to have T2DM.

5.3.2 Indicators of complications in diabetes

The complications of DM were identified from the HDR and Causes-of-Death Register, using the ICD-9 and ICD-10 codes. All symptomatic complications that were considered in this study (ACS, ischaemic stroke and LEA) are treated in hospital in Finland. No attempt was made to identify clinically silent coronary or stroke events.

Nonfatal ACSs, including myocardial infarction and unstable angina pectoris, were identified with the ICD-9 codes 410 and 4110 and the ICD-10 codes I20.0, I21 and I22 in the HDR. The fatal cases were identified with the ICD-9 codes 410–414 and 798 and the ICD-10 codes I20–I25, I46, R96 and R98 in the Causes-of-Death Register. The vague codes 798, I46, R96 and R98 are seldom used in Finland and hardly ever without an autopsy. They were included, however, for the sake of completeness, because the majority of these cases are of coronary origin.

Ischaemic strokes were identified with the ICD-9 codes 433–434 and 436 (excluding codes 4330X, 4331X, 4349X) and the ICD-10 codes I63–I64 (excluding code I63.6). The FINSTROKE study has shown that towards the mid-1990s, neuroimaging and/or autopsy have been performed on practically all patients with a symptomatic stroke (178).This has enabled a reliable distinction between the haemorrhagic and ischaemic stroke types, as also shown by validation studies (176).

CV deaths were identified from the Causes-of-Death Register with the ICD-9 codes 410–414, 798, 430–434, 436 and 438 and the ICD-10 codes I20–I25, I46, R96, R98, I60–I66 and I69 (except for code I63.6) when used as the underlying or direct cause of death. Of the contributing causes of death, we included the ICD-9 codes 410 and 430–434 (except for the codes 4330X, 4331X, 4339X and 4349X) and the ICD-10 codes I21–22 and I60–64 (except for the code I63.6).

LEAs were identified from the HDR by the surgical codes of the Nordic Medico-Statistical Committee (NOMESCO). Minor amputations were identified by the surgical codes NHQ30 and NHQ40 and major amputations by the codes NGQ10, NGQ20, NHQ10 and NHQ20.

In the ACS and ischaemic stroke studies, we focused specifically on the first event. In ACS and ischaemic stroke, it was defined as a 4-year incident-free period before the event. We estimated from our material that this 4-year period left us with about 8% falsely diagnosed

`first´ ACS events and about 11–12% falsely diagnosed `first´ ischaemic stroke events. The 4-year rule was chosen because it resulted in fair accuracy, considering our study length. All patients who had an ACS, ischaemic stroke or transient ischaemic attack (TIA) before DM diagnosis were excluded from the material.

In the ACS and ischaemic stroke studies comparison of the CF was made with the nondiabetic population. The comparison data came from the National Cardiovascular Disease Register (CVDR), which is based on record linkage of the HDR and the Causes-of-Death Register. The CVDR covers all ACS and ischaemic stroke events in Finland that have led to hospitalization or death. The register has been described in detail (179,180). The same ICD codes and the same definition for the first ACS events were used in this comparison material as in the diabetic material. Since we had no personal ID available in our DM register, we used probability-based linkage of our DM register and the National CVDR to identify and remove diabetic persons from the National CVDR. For 45 persons (0.1% of patients with DM) in the ACS study and for 41 persons (0.2% of patients with DM) in the ischaemic stroke study, the linkage failed and these persons were excluded from the study population. The numbers of the population with DM and comparison population for each study year are presented in Table 2.

Table 2. Number of all persons with diabetes, persons with type 2 diabetes (T2DM) and nondiabetic population (comparison population) in the age group of 35–94 years at the end of each year during 1988–2002 in Finland.

Year	Population with diabetes			Population with T2DM			Nondiabetic population		
	Number	% women	Average age (years)	Number	% women	Average age (years)	Number	% women	Average age (years)
1988	76 620	58.9	65.7	68 714	61.1	68.2	2 479 294	53.8	54.3
1989	85 135	58.3	66.3	76 617	60.4	68.7	2 505 789	53.7	54.4
1990	95 790	57.7	66.8	86 598	59.6	69.1	2 529 477	53.6	54.4
1991	100 481	56.6	66.6	90 583	58.5	68.9	2 561 843	53.5	54.4
1992	104 709	55.6	66.5	94 102	57.5	68.8	2 590 106	53.5	54.5
1993	108 971	54.8	66.4	97 698	56.6	68.7	2 613 158	53.4	54.6
1994	111 511	54.0	66.5	99 546	55.8	68.9	2 641 716	53.3	54.7
1995	113 894	53.4	66.5	101 390	55.1	67.0	2 669 284	53.3	54.8
1996	117 920	52.7	66.4	104 938	54.2	68.9	2 695 000	53.2	54.9
1997	123 142	52.0	66.4	109 695	53.4	68.8	2 719 912	53.1	55.0
1998	128 213	51.4	66.4	114 237	52.7	68.7	2 745 653	53.1	55.1
1999	134 061	50.8	66.3	119 532	51.9	68.6	2 768 647	53.1	55.2
2000	142 698	50.1	66.2	127 623	51.1	68.4	2 786 526	53.0	55.4
2001	152 573	49.5	66.1	136 937	50.3	68.2	2 804 953	53.0	55.5
2002	165 288	49.0	66.0	149 077	49.6	68.0	2 818 528	52.9	55.7

5.4 Statistical methods

5.4.1 Case fatality

The prehospital, 28-day and total 1-year CFs of the first ACS were counted, as well as the 28-day and total 1-year CFs for the first ischaemic stroke among patients with T2DM. Comparisons were made with persons without DM, using data from the National CVDR. Age-standardization was made, using weights derived from the age distribution of myocardial infarction and stroke patients in the myocardial infarction and stroke registers of the WHO MONICA Project (181,182).

The trends in prehospital coronary deaths were analysed using logistic regression and ORs (per1-year increment in time). HRs for 0–27-day and 28–364-day CV deaths after the first ACS and the first ischaemic stroke were computed separately for men and women with T2DM in four different age groups (35–64, 65–74, 75–84 and 85–94 years), and again comparing the results with the nondiabetic population. The variables of main interest were the study year, DM status (nondiabetic vs. T2DM) and the study year by DM status interaction, which was used to evaluate whether the CF trends differed between nondiabetic persons and persons with T2DM. The models were adjusted for age in 5-year age groups and for the university hospital district. In analysing trends in total 28-day CV CF and 28–364-day CF, we took the survival times into account, using Cox proportional hazards regression and HRs. The time scale for Cox models in the 28-day CF started from the date of hospitalization. The statistical analyses were carried out, using SAS software version 9.1.3 (SAS Institute Inc., Cary, NC, USA).

5.4.2 Incidence rates

The rates of first amputations were counted for each year from 1988 to 2002 both for men and women. The age- and sex-standardized incidence rates of first amputations were expressed per 100 000 persons with DM, while for regional comparison the data covering the 20 hospital districts were clustered in 3-year periods to stabilize variation in small hospital districts. The incidence of lower extremity-vascular surgery was compared with amputation rate in 14 hospital districts with the highest prevalence of DM.

The incidence rates of the first ACS and ischaemic stroke among patients with T2DM were counted separately for men and women in two age groups: 35–74 years and 75–94 years. For comparison, the rates were also counted for nondiabetic persons, using data from the National CVDR. The rates were age-standardized, using the European standard population as a standard (183).

5.4.3 Population-attributable fraction

The number of patients with DM and the numbers of first ACS and ischaemic stroke events and PAF due to DM were calculated for each year separately for men and women from 1992 to 2002. All patients in the age range 25–80 years for each year were included in the study. All calculations were made by full calendar years; if DM was diagnosed after the CVD event during the same calendar year, the event was considered to be a diabetic event. Annual population counts were obtained from the National Population Information System (http://pxweb2.stat.fi/database/StatFin/vrm/vaerak/vaerak_fi.asp). The PAF due to DM was also counted by combining the figures for both CV events, i.e. either the first ACS or the first ischaemic stroke for a patient with DM.

The annual PAF with 95% CIs of first ACS and first ischaemic stroke due to DM were calculated according to the formula PAF = [[Pe*(RR–1)/{1+[Pe*(RR–1)]}]]*100, where RR is the risk ratio and Pe is the estimate of population exposure (184). The use of the formula is demonstrated in Example 1. The trends for PAF were estimated, using log-linear regression models with the year as an independent variable. We also calculated whether PAF differed by age group (25–54, 55–64 and 65–80 years) in both sexes.

Example 1. Demonstrating the use of the PAF formula.

> When the RR for the first nontraumatic LEA is 6.0 in persons with DM compared with nondiabetic persons and 8% of the population present with DM, the PAF of the first nontraumatic LEA is [[0.08*(6–1)/{1+[0.08*(6–1)]}]]*100 = 28.6%.

6. RESULTS

6.1 Case fatality of acute coronary syndromes (I)

Among the 222 940 patients 35–94 years of age with T2DM, 18 076 men and 21 295 women had their first ACS between the years 1992 and 2001. Patients with T2DM died of CV causes more often than nondiabetic patients. The 1-year fatality proportion in this age group was among men with T2DM 65.2% (95% CI 65.0–65.5%), when it was 56.5% (95% CI 56.4–56.6%) among nondiabetic men. The corresponding figures for women were 61.0% (95% CI 60.4–61.5%) and 48.3% (95% CI 48.2–48.5%).

The fatality proportion analyses showed similar differences, when separate analyses were made in the age groups 35–74 years and 75–94 years. The biggest difference was among women 35–74 years of age, in whom the 1-year fatality proportion difference was 17.3 percentage points higher in women with T2DM (Table 3, reformulated from Table 1 in I).

Table 3. All persons treated for type 2 diabetes mellitus (T2DM) in the age group 35–74 years in Finland, their first acute coronary syndrome (ACS) between January 1, 1992 and November 30, 2002, and numbers and proportions with fatal outcome compared with the same information on nondiabetic patients identified from the National Cardiovascular Disease Register for the period 1992–2002.

		Patients with T2DM		Nondiabetic patients	
		Men	Women	Men	Women
Population	Number	92 371	85 601	1 135 862	1 211 343
First ACS	Number	12 358	7038	70 714	26 106
ACS with fatal outcome Prehospital	Number	3274	1229	20 877	5216
	Fatality proportion (%) (95% CI)	27.1 (27.0–27.2)	18.7 (18.5–18.8)	29.7 (29.7–29.8)	19.8 (19.7–19.8)
ACS with fatal outcome Total 28-day	Number	6269	3131	28 336	8300
	Fatality proportion (%) (95% CI)	50.3 (50.2–50.5)	42.1 (41.9–42.2)	41.0 (41.0–41.1)	30.1 (30.0–30.1)
ACS with fatal outcome Total 1-year	Number	6563	3544	28 864	8825
	Fatality proportion (%) (95% CI)	56.5 (56.4–56.6)	50.3 (50.2–50.5)	44.5 (44.4–44.5)	33.0 (32.9–33.0)

The total 28-day and 1-year fatality proportions were significantly higher statistically in both age groups and among both genders in the diabetic group, but the prehospital CF was significantly lower among patients with T2DM in both genders and age groups (Table 1 in I). Figure 4 shows the cumulative CF during the prehospital, 28-day and 1-year periods following the first ACS event. The figure is based on further analysis of data in I.

Figure 4. Cumulative case fatality after the first acute coronary syndrome among men and women with type 2 diabetes (T2DM) and without diabetes (non-DM) in Finland during the years 1992–2002.
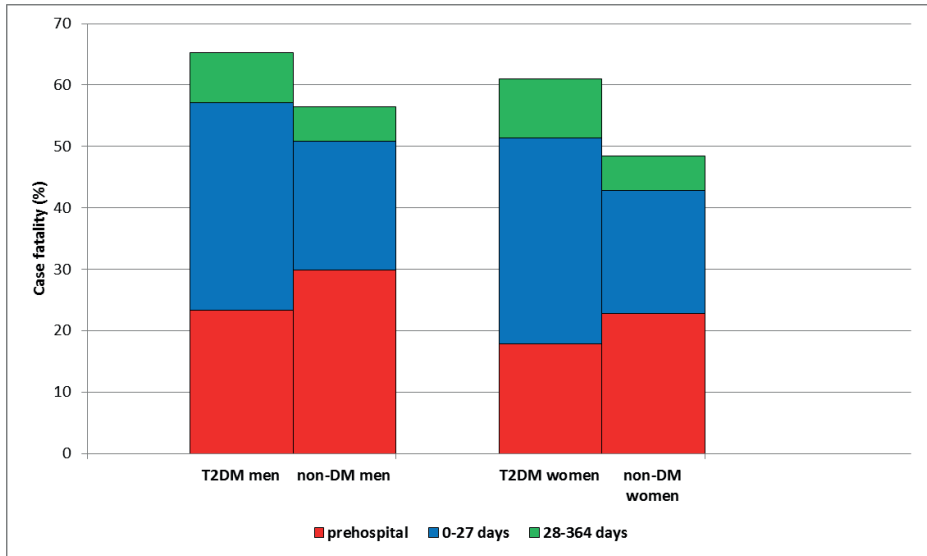
The prehospital CF was higher among men than women, but the difference disappeared after the age of 85. This change occurred both in persons with T2DM and those without DM (Table 2 in I).

Downward trends in prehospital CF were seen during the study period in both genders and in all four age groups, both among patients with T2DM and without DM with their first ACS (Fig. 1 in I). Testing the OR of DM by study year interactions showed that the trends in T2DM did not differ from those in nondiabetic patients, except for women 85–94 years of age, in whom the data suggested a steeper decline in women with T2DM. In the age group 35–64 years the OR for T2DM was nonsignificantly higher than 1.0, but after the age of 65 it was significantly less than 1.0 and became smaller in the older age groups.

The total 28-day CV CF of ACS was significantly higher among T2DM patients in all age groups studied, except the oldest group of persons in the age group 84–95 years (Fig. 2 in I). In the age group 35–64 years, T2DM was associated with 34% higher 28-day CF in men and 69% higher CF in women. The 28-day CF of ACS decreased significantly, both in patients with T2DM and in nondiabetic patients in both sexes and in all age groups. The downward trends did not differ between patients with T2DM and nondiabetic patients.

Among the 28-day survivors, the age-standardized 1-year CV CF decreased significantly both among persons with T2DM and among nondiabetic patients with their first ACS (Fig. 3 in I). The trends did not differ between T2DM and nondiabetic patients. The RR remained considerably higher in patients with T2DM, especially in the youngest age group of 35–64 years. The RR for men was 2.87 (95% CI 2.19–3.75) and for women 5.84 (95% CI 3.70–9.23).

6.2 Case fatality of ischaemic strokes (II)

Among the 222 940 patients 35–94 years of age with T2DM, 9593 first ischaemic strokes among men and 13 504 among women were observed during the years 1992–2002 (Fig. 5). The figure is based on further analysis of data in II. During the study years, 1.4–2.4% of patients with T2DM had their first ischaemic stroke each year. More than a third of them died from CV causes within a year after the stroke. Women had higher CFs of the first ischaemic stroke than men.

Figure 5. Cumulative case fatality after the first ischaemic stroke among men and women with type 2 diabetes (T2DM) and without diabetes (non-DM) in Finland during the years 1992–2002.
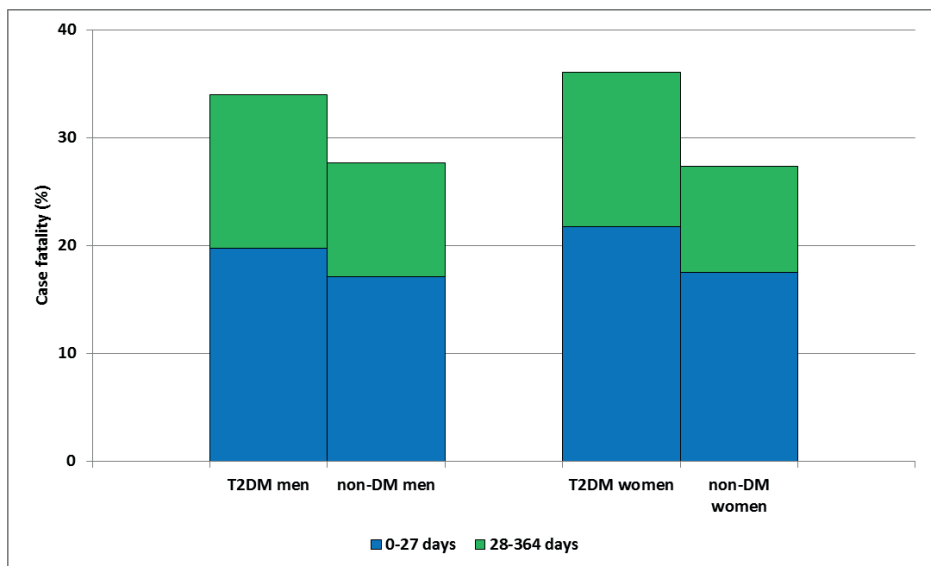
Both the 28-day and 1-year CV CFs of stroke were higher among persons with T2DM in both sexes than in the nondiabetic population (Table 2 in II). The 28-day CF of ischaemic stroke was 1.1–1.3 times higher among T2DM patients than in nondiabetic patients, depending on gender and age group. The 1-year CF of ischaemic stroke of the 28-day survivors was 1.4–2.2 times higher in patients with T2DM than in nondiabetic persons. The difference was smallest in the younger age group of men (35–75 years) and biggest in the younger age group of

women. The total 1-year CV CF of stroke was 1.2–1.6 times higher among patients with T2DM than in nondiabetic persons.

There was a clear downward trend in the CV CF during days 0–27 and 28–364 of the 28-day survivors after the first ischaemic stroke both in persons with T2DM and nondiabetic persons (Figs. 2 and 3 in II). The trends were statistically significant in the age groups 35–74 years and 75–94 years and in both genders, but no difference in trends was seen between patients with T2DM and nondiabetic patients.

6.3 Lower-extremity amputations (III)

Among the 308 447 diabetic persons, there were 11 070 patients who had an LEA and 9530 persons with DM who had a vascular operation (endovascular procedures were not included) during 1988–2002. The crude rate of first amputations decreased from 924 to 387 per 100 000 persons with DM (Fig. 2 in III). The decrease was similar in men and women. We found major differences in the pace of development between hospital districts. The ratio of minor and major amputations showed a positive development during the study period (Table 2 in III). The rate of first diabetic major amputations decreased rapidly in the Finnish population (Fig. 6). The figure is based on further analysis of data in III.

Figure 6. Rates of first diabetic major amputations during the years 1988–2002 in Finland.
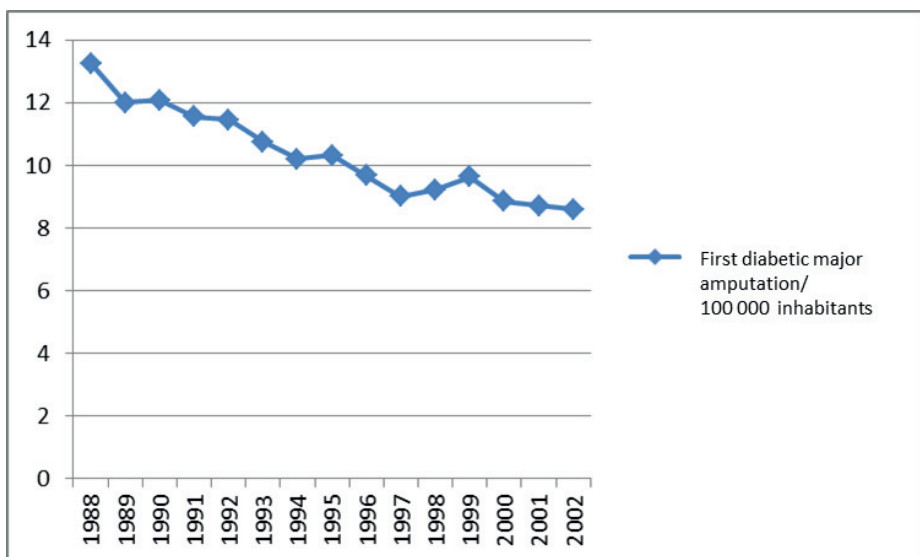
The age- and gender-adjusted indexed incidence of first amputations varied up to 3-fold between different hospital districts during 2000–2002 (Table 1 in III). The study showed a clear inverse association between the incidence of first major amputations and first vascular operation (r = -0.771, p < 0.001). The association was even stronger in comparing the infrapopliteal reconstructions (r = -0.793, p < 0.0001).

6.4 Population-attributable fraction of acute coronary syndrome (IV)

The number of men treated for DM increased from 37 073 to 69 158 between 1992 and 2002. Among women, the increase was from 42 485 to 57 372. Despite this rapid increase in the number of persons treated for DM, the annual numbers of first ACS events among persons with DM increased only slowly among men and decreased among women (Fig. 7). The figure is based on further analysis of data in IV. The PAF of the first ACS, due to DM, increased among men from 11.6% (95% CI 10.9–12.3%) to 15.0% (95% CI 14.2–15.8%), p for trend < 0.0001 from 1992 to 2002. Among women, the PAF decreased nonsignificantly from 22.0% (95% CI 20.9–23.2%) to 20.6% (95% CI 19.4–21.8%), p for trend 0.102 (Table 3 in IV). The trends in PAF were significantly different between the sexes (p < 0.001 for the year by sex interaction) (Fig. 8).

Figure 7. Prevalence of diabetes (DM) among Finnish men and women and incidence of first acute coronary syndrome (ACS) in the population with diabetes during the years 1992–2002.
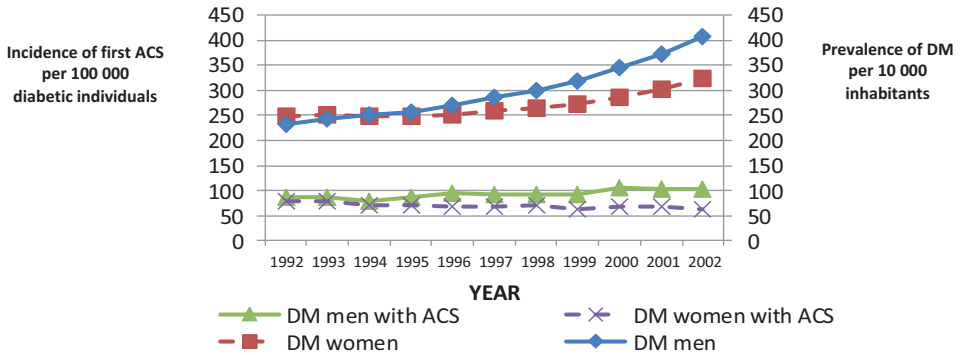
Figure 8. Population-attributable fraction (PAF) of the first acute coronary syndrome (ACS) due to diabetes during 1992–2002 in Finland.
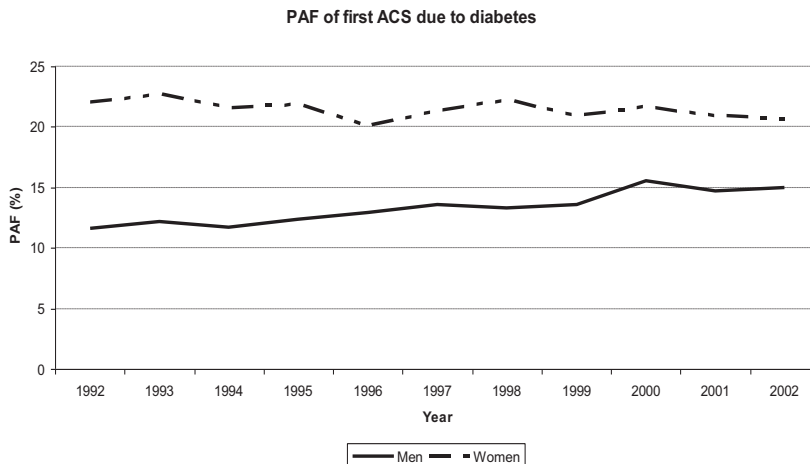
6.5 Population-attributable fraction of ischaemic stroke (IV)

As described above in chapter 6.4, the prevalence of DM increased substantially from 1992 to 2002. Still, the annual incidence of first ischaemic stroke remained almost stable among men and decreased among women with DM (Fig. 9). The figure is based on further analysis of data in IV.

Figure 9. Prevalence of diabetes (DM) among Finnish men and women and incidence of first ischaemic stroke event in the diabetic population during 1992–2002.
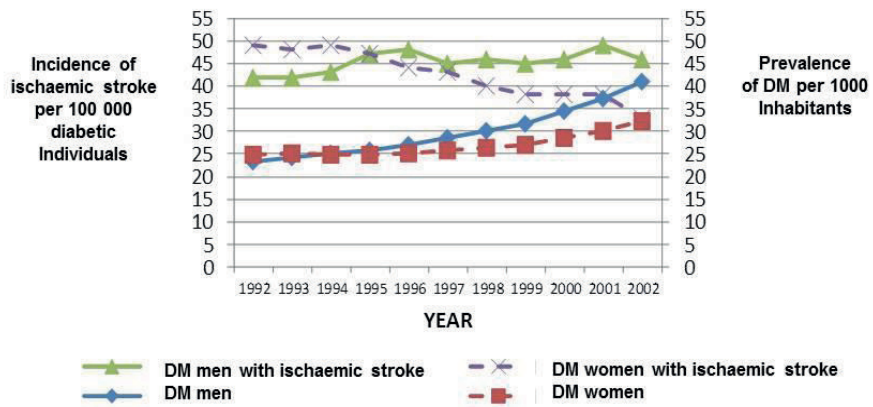
Figure 10. Population-attributable fraction (PAF) of the first ischaemic stroke event due to diabetes from 1992 to 2002 in Finland.
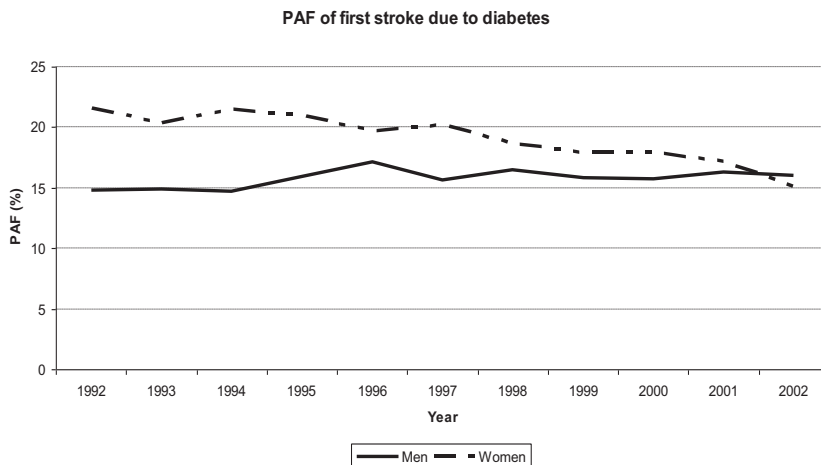
The PAF of the first ischaemic stroke due to DM increased among men from 14.8% (95% CI 13.6–16.0%) in 1992 to 16.0% (95% CI 14.7–17.3%) in 2002, p for trend 0.065, while the PAF

for women decreased from 21.5% (95% CI 20.1–22.9%) to 15.1% (95% CI 13.7–16.4%), p for trend < 0.001. Again, the trends in PAF were significantly different between the sexes (p < 0.001 for the year by sex interaction) (Fig. 10).

6.4 Population-attributable fraction of cardiovascular diseases (IV)

The PAF of the first CVD event (either ACS or ischaemic stroke) due to DM showed an upward trend among men from 11.4% (95% CI 10.8–12.0%) to 13.8% (95% CI 13.2–14.5%), p for trend < 0.0001, and a downward trend among women from 20.1% (95% CI 19.2–21.0%) to 16.9% (95% CI 15.9–17.8%), p for trend 0.0005 (Table 3 in IV). These trends were significantly different between the sexes (p < 0.001 for the year by sex interaction) (Fig. 11). The change in PAF occurred mainly among men under 65 years, while in women the change occurred in all age groups. The PAF clearly increased with age in women, whereas in men the increase was modest (Table 4 in IV).

Figure 11. Population-attributable fraction (PAF) of the first cardiovascular disease (CVD) event of either acute coronary syndrome or ischaemic stroke due to diabetes during 1992–2002 in Finland.
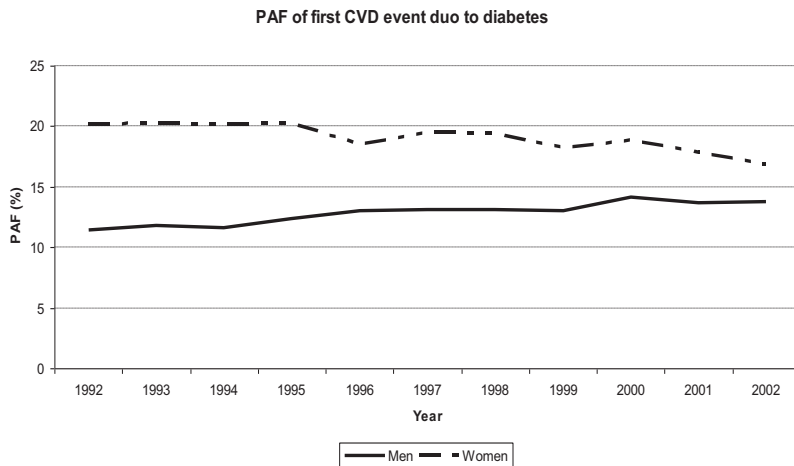
7. DISCUSSION

7.1 Summary of the main findings

This study confirmed that DM is a major risk factor for CVD. The PAF of the first ACS due to DM was 15% among men in 2002, with a significant increase since 1992. The PAF of the first ACS due to DM among women was 20.6% in 2002, with a nonsignificant decrease since 1992. The PAF of the first ischaemic stroke due to diabetes was 16.0% among men and 15.1% among women in 2002. These numbers were preceded by a very significant decrease among women and a nonsignificant increase among men since 1992.

Almost 18% of T2DM patients had their first ACS during the study period and about 60% of ACS patients with DM died of CV causes within a year. Ischaemic stroke was also common among T2DM patients. Between 1.4% and 2.4% of patients with T2DM had their first ischaemic stroke each year. More than a third of them died of CV causes within a year of their stroke.

Men with DM had higher prehospital, 28-day and total 1-year CF of the first ACS event in all age groups than women with DM. Both men and women with DM had higher 1-year CF of the first ACS event than their nondiabetic counterparts. The difference was biggest in the younger age group (35–74 years) of women, in whom the difference in 1-year fatality proportions was 17.3 percentage points. The CF decreased significantly in all groups studied and there was no difference in the pace of development between populations with and without DM from 1992 to 2002.

Women with T2DM had somewhat higher CF of the first ischaemic stroke than men with T2DM. Patients with T2DM had a higher CV CF than nondiabetic patients both in the acute phase (1.1–1.3 times higher) and especially during the first year after the acute phase of stroke (1.4–2.2 times higher). The excess 28-day CF caused by T2DM was similar in both genders and in each age group, but the excess CF for the 28-day survivors was highest in the younger age group of women (HR 2.2, 95% CI 1.7–2.7).

Diabetes remains a major risk for LEA, although the rate of major amputations has drastically decreased from 1988 to 2002 (Fig. 6).

7.2 Study populations and methods

7.2.1 Study populations

This study was based on the nationwide Finnish registers of hospital discharges, reimbursements for the costs of medicines and causes of death. With the help of the personal ID the registers could be linked at the individual level. This setup enabled research that is unique in international comparison, because it allowed us to study the entire

population in Finland with long follow-up times. One can notice the benefits in comparing our results with those published in the international literature, in which most studies were based on very limited populations.

DM diagnosis was mainly based on the use of hypoglycaemic medication, and to some extent on the information of the HDR. Information on the hypoglycaemic medication used came from the reimbursement registers of the Social Insurance Institute. These registers comprehensively covered patients using hypoglycaemic medication. The high level of coverage was due to the 100% special reimbursement of medicine costs if the disease was certified by a physician. The study data reached back to 1964 to identify these persons. Since 1994, all prescribed purchases of hypoglycaemic medication have also been registered, and since hypoglycaemic medication is not available without a prescription, the register information is comprehensive. It must be pointed out that the reimbursement registers of the Social Insurance Institute do not include diabetic patients treated with diet only. Furthermore, the registers do not include permanently institutionalized patients who receive their medications from their institutes. Diseases of patients in the latter group are, however, included in the HDR. Some patients with DM who are treated with diet only may have been included in the HDR or the Causes-of-Death Register. It is, however, likely that this has occurred mainly in cases, in which DM has been a contributing cause for hospital treatment or death. Most patients from these two groups were thus not included in the diabetic population.

Determining the type of DM involved some uncertainty, because we had to use indirect reasoning to do so. The type of DM was used only in the CF analyses, in which we were specifically interested in T2DM patients. The type was determined, based on age at the time of first diagnosis and the type of treatment given as described in the Methods section.

The validity of the HDR and CVDR diagnoses in CVDs has been shown elsewhere (175,176). The FINSTROKE study has shown that towards the mid-1990s neuroimaging and/or autopsy have been performed on practically all patients with a symptomatic stroke (178).This has enabled reliable distinction between haemorrhagic and ischaemic stroke types (176), thus also focusing our interest in ischaemic strokes. We excluded all persons who had an ACS or stroke event before DM was mentioned for the first time in the registers and all those who were living abroad, according to the reimbursement register records.

We determined the first-ever event of ACS or ischaemic stroke to be a 4-year event-free period. This 4-year period was kept the same for the later study years to avoid creating systematic bias. We estimated from our material that a 4-year period left us with about 8% falsely designated first ACS events and about 11–12% falsely designated first strokes. A 2-year period would have given us about 15% falsely designated first ACS events, while a 7-year period would still have left us with about 3% false first ACS events.

For comparison, the same analyses were made for the nondiabetic persons in the National CVDR. This register is based on recorded linkage of the HDR, the Causes-of-Death Register and the National Drug Reimbursement Register. The CVDR covers all ACS and stroke events

in Finland that have led to hospitalization or death. The validity of the register has been described (175,176) and the summary tables as well as the methodological background are available in the Internet (185). The same ICD codes and the same definition for the first ACS and first ischaemic stroke event were used in this comparison material as in the diabetic material. Probability-based linkage of our DM register and the National CVDR was used to identify and remove persons with known DM from the National CVDR, because there was no personal ID available in the DM register. The linkage failed for 45 persons in the ACS analysis (0.1% of the patients with DM) and 41 persons in the stroke analysis (0.2% of patients with DM). These patients were excluded from the study population.

As described above, the national registers allowed us to build a unique study population, and with careful definitions of various situations we believe we have been able to avoid many biases and have been able to form a basis for high-quality international research. A major limitation still remained: the study population did not include all patients who were treated for their DM with diet only, as described previously. Those presented with DM, but who were undiagnosed by the time of the study, were also not included.

7.2.2 Methods

The CF proportions of the first ACS and first ischaemic stroke were counted for persons 35–94 years of age divided into two age groups. The ORs of prehospital deaths and the HRs of 0–27- and 28–365-day fatalities were counted in four age groups. The division into four age groups proved to be useful, because it added information. Published articles have often included all diabetic persons in the analyses, including those younger and older, than we did. If we had also included all diabetic persons in the analysis, it would have helped in international comparisons.

Dividing the CF analyses into the three periods (prehospital, 0–27-day and 28–364-day) gave valuable information on problems in the chain of care. An addition to this would be to also analyse in-hospital and posthospital periods separately. In-hospital analysis is, however, not unambiguous in register research.

PAF analyses are valuable from the health political standpoint, because macroscale health problems can be detected and followed by this method. PAFs are recommended for use in assessing the potential impact of public health interventions (186). Interestingly, very few PAF analyses of DM have been reported: only a few on the PAF of CVD due to DM (168,169), some on CHD (170–172), one on stroke (187) and a few on LEAs (155,174). Unfortunately, the registers we used did not allow more widespread analysis of the PAFs of different risk factors in CVD events.

In using the age scale 25–80 years, we may have excluded some of the additional burden DM causes in elderly people, especially in women. Again, one should consider also including elderly people for easier future international comparisons.

7.3 Case fatality of acute coronary syndromes

Our study showed an RR of 1.33 for men and 1.48 for women with T2DM compared with the nondiabetic population in the younger age group of 35–74 years in the 1-year total CF. These figures are in line with studies from Australia in the late 1980s (141). The study in Finland that investigated the first ACS in patients 25–64 years of age showed 1-year HRs for 28-day survivors of 1.97 (95% CI 1.25–3.12) among men with DM and 4.17 (95% CI 2.05–8.51) among women with DM (142). The corresponding figures in our study for the age group of 35–65 years in men and women with T2DM were 2.87 (95% CI 2.19–3.75) and 5.84 (95% CI 3.70–9.23). Direct comparison of the figures is not possible, due to the difference in age groups and the fact that the previous study also included patients with T1DM. It seems, however, that very little positive development has been accomplished, although the authors of the 1988–1992 study recommended vigorous primary and secondary preventive measures (142).

Our study showed a statistically significant difference between T2DM patients and nondiabetic patients in both genders and age groups in the total 28-day and 1-year CF after the first ACS. A study in the Netherlands was not able, after multivariate adjustment, to show any difference in 28-day CF, but they did show a difference in 1-year CF (143). A study in Germany that followed up 701 diabetic patients who had an ACS during 1998–2003 was likewise unable to find any difference between patients with DM and nondiabetic patients in 28-day CF, but they did find an additional risk for 28-day survivors with DM in long-term follow-up (RR for men with DM 1.57 (95% CI 1.18–2.10) and women with DM 2.91 (95% CI 1.82–4.65) (188).

The literature shows that results of short-term care do not differ greatly, but long-term prognosis after the first ACS is worse for patients with DM. Our results showed that the prehospital fatality proportion is lower among T2DM patients than among nondiabetic persons, but at 28 days the CF among T2DM patients was already significantly higher. This is in line with the results from the Berlin Myocardial Infarction Registry, which collected information from 25 hospitals in Berlin between 1999 and 2002. The authors reported higher hospital mortality after an ACS event for women with DM than men, OR 2.28 (CI 95% 1.42–3.68), for women with DM compared with nondiabetic women, OR 2.92 (95% CI 1.75–4.87) and no difference for men with DM compared with nondiabetic men (189).

An interesting and important aspect is, whether any change has occurred in the CF after the first ACS among patients with DM compared with nondiabetic patients, especially when the decline has been shown in the general population (7,190–194). The follow-up of the NHANES study suggested that the trends have not been favourable among patients with DM (135). Between the periods 1971–1975 and 1982–1984, nondiabetic men showed a 36.4% decrease in age-adjusted heart disease mortality compared with a 13.1% decrease for men with DM. The decrease was 27% in nondiabetic women, but there was an increase of 23% in women with DM (135). A registry study from northern Sweden was not able to show a decrease in the 28-day CF among men or women with DM, but it did show a significant decrease among nondiabetic persons in the age group 35–64 years from 1989 to 2000 (144). The 1-year

mortality rate also decreased significantly among nondiabetic men and women, but not among men and women with DM. However, there was a downward trend among women with DM in both 28-day and 1-year CF (144).

In our study we found that in all age groups the prehospital survival improved from 1992 to 2002 and there was no difference in development between the T2DM population and the nondiabetic population, except for women with DM in the age group 85–94 years, whose prognosis improved more rapidly than in nondiabetic women of the same age. Again, the prognosis for 28-day survival and 1-year survival of 28-day survivors improved in all age groups of both genders and there was no difference in outcome between the T2DM and nondiabetic populations. In this respect, the results are somewhat better than those reported in other studies. The difference is probably again due to the fact that this study followed up the first ACS events, while many other studies followed any ACS event.

The prehospital CF remained lower in T2DM patients than in nondiabetic patients in both genders and all age groups, except in the youngest group of 35–64 years. This is interesting, because it is often pointed out that in DM myocardial infarctions can occur with mild and confusing symptoms (195). DM is also an independent predictor of delay in ACS care (196). The development of ACS may be different in persons with DM and nondiabetic persons and this could explain the lower prehospital CF and higher long-term fatality. For instance, intravascular ultrasound has demonstrated that patients with DM tend to have a higher occurrence of vulnerable plaques than patients without DM (197). Poorer prognosis in persons with DM has resulted in special recommendations for improving the care of patients with DM in intensive care units (198). An influencing factor is also that many elderly patients with DM are already hospitalized for various reasons and therefore cannot die before hospitalization.

A study from the Register of Information and Knowledge about Swedish Heart Intensive care Admissions showed that after adjusting for dissimilarities in baseline characteristics between ACS patients with and without DM, those with DM were significantly less likely to be treated with reperfusion therapy (OR 0.83), heparins (OR 0.88), statins (OR 0.88) or to be revascularized within 14 days from hospital discharge (OR 0.86) (199). Only the use of angiotensin-converting enzyme (ACE) inhibitors was more prevalent among patients with DM than in nondiabetic patients (OR 1.45), although all these treatments have equal benefit in patients with DM and nondiabetic patients (199). The conservative treatment schemes may be reflected in the Swedish prognosis figures: patients with DM had an adjusted relative 1-year mortality risk after myocardial infarction of 1.44 (95% CI 1.36–1.52) in 1995–1998 and 1.31 (95% CI 1.24–1.38) in 1999–2002 (200). Similar insufficient treatment was also reported from hospitals in Finland (201). Insufficient treatment of patients with DM has also been reported from Canada, where patients with DM were less likely to undergo coronary angiography (52.5% vs. 57%, p < 0.001) or revascularization (28.4% vs. 33.4%, p < 0.001). Compared with the group without DM, patients with DM had higher unadjusted rates of in-hospital mortality (3.0% vs. 1.6%, p < 0.001) (202).

In our study, the fatality after hospital entry of the first ACS remained much higher in T2DM patients than in nondiabetic patients. This can be explained by the effect of DM itself, the differences in treatment in the hospital or primary and secondary prevention in outpatient care. Lipid-lowering therapy in T2DM decreases the incidence of CHD (203). CHD is also prevented by treatment for BP (88) and blood glucose (204). A study in Finland, monitoring secondary prevention in CHD showed that patients with DM used the same type of secondary prevention treatment as did nondiabetic patients: antithrombotic medication in about 90%, a beta-blocker in about 80% and a statin in about 60% (205). A recent study in Finland showed that beta-blocker use was high in the CHD populations with and without DM in 1997–2002, while ACE inhibitor and angiotensin II antagonist use increased and remained higher among patients with DM (206). More than half of men and women with DM used ACE inhibitors and one out of five used angiotensin II antagonists in 2002. Lipid-lowering medication use increased, especially among women with DM. Among men with DM the use of lipid-lowering medication remained lower than among nondiabetic men (206). Secondary prevention can also differ between genders. A study in Austria found that men were treated more favourably in all parameters measured and invasive treatments were used more often (207). A study in 12 countries in Europe and North America showed that 48.1% of those with DM were not at the total cholesterol target level compared with 58% of those without DM (208). This is in line with the Finnish results: 59% of T2DM persons had LDL-C ≤ 2.5 mmol/l and 27% had BP less than 135/85 mmHg (15).

In referring the CF findings after the first ACS, development in outcomes among T2DM patients was favourable in Finland during the 1990s. Some positive development has occurred in treatment activity, but special effort is still needed in primary and secondary prevention of CV risk factors.

7.4 Case fatality of ischaemic strokes

We found that the 28-day CF was 1.1–1.3 times higher and the 1-year CF of 28-day survivors was 1.4–2.2 times higher in patients with T2DM than in nondiabetic patients after the first ischaemic stroke. The overall incidence of stroke has declined in Finland and the prognosis after stroke also improved during the period 1991–2002 (8), but in absolute numbers the annual incidence of first stroke among patients with DM remained stable in Finland in the 1990s (29). DM affects about one fourth of stroke patients (149,150) and stroke is much more common in persons with DM than in nondiabetic persons, 1.5–8 times depending on age and gender, and more common in women (77–79,209). Research on prognosis after stroke in a person with DM has produced contrasting results in different countries. Results from Finland suggest a poorer prognosis for persons with DM; the 28-day CF was higher in patients with DM than in nondiabetic patients (20.0% vs. 16.9%, p = 0.020) (150). This register study considered all strokes, not only the first.

We found a significant decrease in CF trends and no difference in trends of T2DM and nondiabetic patients. This was in line with the results that Booth et al. showed in their study; patients with DM experienced reductions in CF related to stroke similar to those without DM

(-17.1% vs. -16.6%, p = 0.9) from 1992 to 2000 (134). Over the same period, the number of DM cases increased from 405 471 to 670 602. Thus, while CVD rates fell, the number of events occurring in this population increased (134). A study in Veterans Administration hospitals in the U.S. followed up 13 925 patients with DM after an ischaemic stroke between 1990 and 1997. The 60-day and 1-year fatality proportions were similar in patients with and without DM (2.9% vs. 2.7%, p = ns and 12.6% vs. 13.1%, p = ns, respectively), but the RR for fatal outcome among patients with DM was 1.15 (95% CI 1.11–1.19, p < 0.001) after controlling for covariates (149). A study from Austria showed similar CF among stroke patients with and without DM (210). A study in Denmark showed that only age was associated with a poor early prognosis after stroke, but DM was associated with poorer late prognosis: OR at 90 days 1.35 and at 1 year 1.33 (211).

A literature search suggests that there is a difference in survival after ischaemic stroke that favours the nondiabetic population, especially over the long term. DM is considered to be the strongest predictor of fatal outcome within 5 years after the stroke (212). This again brings up the question about time trends when the results of stroke patients with and without DM are compared. Are the patients with DM catching up on the additional risk gap they have? The literature furnishes no answers to this question. Our results suggest that the prognosis of stroke in patients with T2DM has improved as it has in nondiabetic patients in Finland, although the gap between patients with DM and nondiabetic patients has remained.

Again the question is raised: does T2DM as such pose the extra burden or are there other factors that could be tackled? The INTERSTROKE study in 22 countries showed that the combined PAR of following risk factors may be responsible for 90% of ischaemic stroke events: hypertension (OR 2.64), current smoking (OR 2.09), waist-to-hip ratio (OR 1.65), diet risk score (OR 1.35), regular physical activity (OR 0.69), DM (OR 1.36), alcohol intake (OR 1.51, for more than 30 drinks per month or binge drinking), psychosocial stress (OR 1.30), depression (OR 1.35), cardiac causes (OR 2.38) and ratio of apolipoproteins B to A1 (OR 1.89) (148). It should be noted, however, that the INTERSTROKE study used a cross-sectional case-control design, which limits these inferences. Nevertheless, modifiable risk factors count greatly and should be better tackled. For instance, only 27% of T2DM patients in Finland reach the BP target of less than 135/85 mmHg (15) and 49.7% are obese (BMI > 30 kg/m²) (213). A study in the U.S. showed that stroke survivors have several risk factors that predispose them to further CV events: 18% of those with hypertension did not receive medication and 55% of those that were treated did not reach the target level of < 140 mmHg, but were an average of 20 mmHg above the target level (214).

Women with T2DM had higher CF proportions in both age groups and time periods considered (0–27 days and 28–364 days after the stroke) than men with T2DM in our study. This could have resulted from the predisposing factors for stroke (hypertension, atrial fibrillation, congestive heart failure and valvular heart disease), which are more common in women (215), or that men have more lacunar infarctions, which have more favourable prognoses, than women (216). It is also possible that women are treated less actively after an ischaemic stroke, as has been the case for female coronary patients in Finland (205).

Our results were in line with those from northern Sweden. Rautio et al. found that there was a significant decrease in the incidence of first strokes among both persons with DM and nondiabetic persons in northern Sweden (79). The CF of the first stroke also decreased significantly in all other groups, except younger women with DM (79). In our study, even this group made significant progress.

In conclusion, we were able to show significant downward trends in the CV 28-day CF and 28–364-day CF of 28-day survivors after the first ischaemic stroke in persons with T2DM. The trends were similar to those in nondiabetic persons and better than in many other reports from other countries.

7.5 Lower-extremity amputations

People with DM have a 5–20-fold higher risk for amputation (155,217,218). Thus, the CV risk caused by DM seems to be highest in the lower extremities. The age-adjusted amputation incidence in the total population of southern Finland fell by 30% from 1990 to 2000 (9). Again, we wanted to know whether the positive trend in the general population also applies to persons with DM.

Reports from other countries have not shown very promising results in the population with DM. A study in Australia was not able to show any change in major amputation rate from the period 1998–1999 to 2007–2008 (219). A study in England likewise found no change in DM-related amputation rate from 2004 to 2008 (154). Both of these studies analysed all amputations, which leaves several uncertainties in interpretation of the results, because several LEAs can be done in the same person.

Our study showed that although there is a wide variation in different areas of Finland, the crude rate of major LEAs shows a strong downward trend. This was in line with a study from Scotland which showed that from 2000 to 2006 the incidence of major amputations fell from 5.1 (95% CI 3.8–6.4) to 2.9 (95% CI 1.9–3.8) per 1000 patients with diabetes (P < 0.05) (220) and from Sweden, where the incidence of major amputations in persons with DM decreased from 16 (95% CI 11–22) to 6.8 (95% CI 6.1–7.5) per 100 000 inhabitants between the first and last 4-year period during 1982–2001 (161). Similar results have been reported from the Veterans Health Administration in the U.S.: age- and sex-standardized first LEA rates decreased by 34% (7.08 per 1000 patients with DM in 2000 to 4.65 per 1000 patients with DM in 2005) (221). The rate of major amputations decreased 36% during the same period (221). We previously showed that the absolute number of amputations among persons with DM in Finland slowly increased from 998 in 1988 to 1224 in 2002 (29). Thus, despite the positive results, we were left with uncertainty. Later we analysed the development in the RR of first major amputations among persons with DM compared with nondiabetic persons (156). The age-standardized RR among men with DM fell from 11.7 (95% CI 10.9–12.4) in 1997–2000 to 7.0 (95% CI 6.5–7.4) in 2004–2007. The change in age-standardized RR for women with DM fell from 8.8 (95% CI 8.3–9.3) to 4.5 (95% CI 4.2–4.8) (Table 4) (156).

Table 4. Relative risk (RR) of the first major amputation among persons with diabetes (men and women separately by age groups) vs. nondiabetic persons during 1997–2000 and 2004–2007 (with permission of Diabetes Care) (156).

	1997–2000 RR (95% CI)	2004–2007 RR (95% CI)
Men by age groups (years)		
30–49	55.5 (42.1–71.9)	35.9 (26.1–48.2)
50–64	22.9 (19.9–26.2)	16.2 (14.2–18.3)
65–74	13.5 (12.1–15.0)	7.4 (6.5–8.3)
75+	7.3 (6.6–8.2)	4.5 (4.0–5.0)
All	11.7 (10.9–12.4)	7.0 (6.5–7.4)
Women by age groups (years)		
30–49	81.1 (54.7–115.8)	55.0 (34.9–82.5)
50–64	29.3 (22.9–37.1)	19.8 (15.5–25.0)
65–74	18.1 (15.9–20.6)	7.1 (5.8–8.5)
75+	6.9 (6.4–7.4)	3.7 (3.4–4.0)
All	8.8 (8.3–9.3)	4.5 (4.2–4.8)

One could expect that smoking increases the amputation rate in a diabetic population in the same manner as it does in the general population (222,223). A study in Japan showed that the OR for amputation among heavy smokers was 2.07 (95% CI 1.11–3.85) in a multivariate analysis among T1DM patients (224). Due to the hazardous effect of smoking on the development of PAD, some of the differences in amputation rates can be explained by the prevalence of smoking. In a study in Finland 12.7% of T2DM patients and 21.1% of T1DM patients were daily smokers in 2008 (213).

A study in the U.S. showed a 2.10 (95% CI 1.17–3.77) RR of LEA for persons with DM, who had the disease before the age of 30 and 1.19 (95% CI 0.57–2.48) for those who contracted the disease after the age of 30 (225). Chronic kidney disease increases the risk for PAD (226).

Diabetic neuropathy is a strong predictor of foot problems. It was estimated that 50% of diabetic foot ulcerations and LEAs can be prevented by identifying the foot at risk and implementing preventive strategies (227). Neuropathy causes the lack of protective

sensation, which allows ulceration in areas of high pressure. Autonomic neuropathy causes dryness of the skin by decreased sweating and therefore vulnerability of the skin to ulcers. Diabetic neuropathy is a result of microangiopathy, in which again hyperglycaemia plays a major role. In 1993 the average HbA1c was 8.8% among patients with DM (228). This partly explains the high incidence of amputations. Much remains to be accomplished in developing the total chain of services to prevent diabetic foot problems and amputations.

7.6 Population-attributable fraction of acute coronary syndrome

Our study showed no change in the PAF of ACS due to DM for women, while we found a significant increase in the PAF for men. The significant change in the male population occurred in the younger age groups of 25–54 years and 55–64 years. Interestingly, at the same time women showed a downward trend that was nonsignificant. The trends in PAF were significantly different between the sexes (p < 0.001 for the year by sex interaction), although the PAF remained higher level among women (20.6% vs. 15.0%). The diverging development for men and women could have been due to the greater increase in obesity among men than among women (229), which has increased the number of cases more in men than in women among people with DM, although recent studies showed that women are now gaining weight at a faster pace (230). Pajunen et al. compared five cohorts from different time periods; the annual increase in body weight among men between 25 and 54 years old remained stable in the range of 0.27–0.47 kg per year over the decades, whereas women belonging to the most recent cohorts (during the 1990s) gained weight in amounts of 0.53–0.63 kg per year, which is more than double the oldest cohort's weight gain of 0.24 kg per year (230). Another, even stronger, explanation for the gender difference could be that we analysed the age group 25–80 years. This could have affected the results, because women tend to have their first ACS event about 10 years later than men (231,232).

The INTERHEART Study showed a PAF of 9.9% for ACS due to DM in 52 countries (131). This is less than our results (15.0% for men and 20.9% for women), but it should be remembered that our study focused on the first event. The difference also reflects the high prevalence of DM in Finland.

7.7 Population-attributable fraction of ischaemic stroke

The development in PAF of ischaemic stroke due to DM followed the same pattern as the PAF of ACS. DM still had a greater influence on PAF among women than among men, but while DM in women is becoming less influential on the PAF of ischaemic stroke, the contrasting situation is occurring among men. This may be due to the increasingly better treatment of women with DM or simply to their compliance with the recommended treatments. The INTERSTROKE Study, which is a cross-sectional case-control study, reported that the PAF of ischaemic stroke due to DM in 22 countries was 5.0% (99% CI 2.6–9.5%) (148). This study, as ours, focused on the first stroke, but the PAF was much smaller than in our study, in which the last study year showed a PAF of 15–16%. One explanation for the

high figures in our study may be high BP, in which treatment goals are seldom reached. A study from Finnish general practice showed that only one fourth of hypertensive patients reached a BP level of 140/85 mmHg (233). It was estimated that 75% of CVD is explained by high BP in patients with DM (90). The INTERSTROKE study estimated that the PAF due to history of BP was 34.6% (99% CI 30.4–39.1%) (148). Concomitant hypertension in DM doubles the risk for stroke (132).

7.8 Population-attributable fraction of cardiovascular diseases

Very few results are available from the last decade on the PAF of CVD due to DM. Our finding, showing an increasing PAF of the first CVD event due to DM for men, was in line with the report from the Framingham Heart Study (168). In the Framingham study, the researchers followed a narrower age group of people (45–64 years) than we did. They examined all CVD events, not only the first ones, and also included TIA, claudication and heart failure, while our material covered the first ACS and stroke events. In the Framingham study, the PAF of CVD was 5.4% (95% CI 3.8–6.9%) during the years 1952–1974 and 8.7% (95% CI 5.9–11.4%) during the years 1975–1998. Most of the change occurred among men as it did in our material in the same age group.

The PAF figures of the later period of the Framingham study are somewhat lower than those in our study population, probably due to the younger age group. The Finnish PAF of CVD due to DM is closer to the figures from Brazil, where the PAF due to DM was 10.1% for CVD mortality and 13.1% for total CVD (234). This study was based on a population cohort of 1019 persons.

PAF analyses gave interesting information on the burden of DM on CVD first events in Finland. The threat of a DM `tsunami´ overloading hospitals treating CVDs seems to some extent exaggerated. The positive development among women, in whom the PAF of CVD is decreasing, seems promising.

7.9 Strengths and limitations of the study

The main strength of our study was that we were able to analyse the development in incidence of macrovascular complications of DM in the entire population of Finland. This was due to the comprehensive register data in the Finnish national registers of hospital treatment, causes of death and medication used. The national registers also enabled us to follow the development for long periods of time. Comprehensive registers of total populations include large numbers of observations with strong statistical power, which also makes it possible to observe weak signals. The existing National CVDR made it possible to make comparisons with the nondiabetic population, which also reinforced our results.

While the strengths of this study came from the comprehensive register materials, the registers also constituted the limitations of the study. The diagnosis of DM was based on the

register information. In most cases the diagnosis was based on the Reimbursement Register or Sales of Medicines Register of the National Social Security Institute, because the other registers (HDR and Causes-of-Death Register) seldom included the diagnosis of DM for those that were treated with diet only. The group of patients with DM who are treated with diet only is continually becoming smaller with modern treatment regimens. Thus, the estimated increase in the prevalence of DM based on the registers was upwardly biased for two reasons. The first was the more active use of hypoglycaemic medications towards the end of the study period. The second reason is the changed definition of DM (12). Nevertheless, most of the increase is likely to be real and due to increasing obesity.

Another limitation is that the registers used are primarily designed for administrative purposes and the diagnoses in them have not been standardized in a scientific manner. There are, however, several published validation studies on CV diagnoses in these registers and their validity has generally been favourable (175,176). As usual in this type of study, we analysed clinically symptomatic ACS and stroke events only. Identifying clinically silent coronary and stroke events is not possible from these data sources.

7.10 Clinical implications

The study results show that persons with DM have benefited from the development of medicine and new therapies in the same way as the nondiabetic population. The rate of change was about the same in both groups, but the difference in outcome remained the same for most of the indicators used.

Many studies have shown that macrovascular complications can often be prevented if the risk factors are aggressively treated. Unfortunately, however, many times the risks are less well treated in the population with DM than in the nondiabetic population. Early, aggressive treatment should be the goal in DM treatment.

We found that often the prognosis of a patient with DM is similar to a nondiabetic patient in the first phase of hospital treatment, but later after the acute event the survival decreases more rapidly in the population with DM. Thus, secondary prevention should be emphasized after a macrovascular event in a person with DM. With active primary and secondary prevention, and treating the total risk load of a person with DM, the risk of CVD events could be lowered drastically.

7.11 Future research needs

Continuous feedback with healthcare producers on acute CV events in the population with DM would be helpful. In principle, this could occur by including information about DM in the National CVDR or, alternatively, enabling annual record linkage between the DM register and CVDR. Since DM is increasing rapidly, the incidences should be counted for the total population.

The CF of the first ACS, stroke or LEA event should be constantly followed up by comparing the results in the populations with and without DM. This would give a good basis for quality evaluations of treatment regimens. Regional analysis, e.g. by university hospital district or hospital district, would give even better grounds for local decision making.

Following up the PAF of CVD events due to DM at intervals of few years is also important. This information forms a strong basis for political decision making in planning resource delivery in society and healthcare. In Finland, the PAF of amputations due to DM should be counted especially, because we did not cover it during our study.

Future studies of all age groups should be included. This would make international comparison easier. The differences between genders should be thoroughly examined. Future studies could also follow up the effect of different medications. The registers we used would allow us, with certain limitations, to study the effects of various hypoglycaemic, BP and lipid-lowering medications. This may help to find answers for why patients with DM progress more poorly than nondiabetic patients. Future registers of ambulatory care will also allow comparison of the influence of risk factors, such as smoking, or various laboratory test results, on the outcomes.

8. CONCLUSIONS

DM is still a major risk factor for CVD in Finland. The PAF of first CVD events due to DM was about 15% in 2002, somewhat less for men (13.8%), but increasing since 1992, and somewhat more for women (16.9%), but decreasing. The PAF of the first ACS increased significantly since 1992 among men and decreased nonsignificantly among women. The PAF of the first ischaemic stroke showed a nonsignificant increase among men since 1992 and a very significant decrease among women. There is no clear explanation for the differences in development among men and women. These should be studied further.

Almost 18% of T2DM patients had their first ACS during the study period and about 60% of ACS patients with T2DM died within a year in CVDs. Ischaemic stroke was also common among patients with T2DM. Between 1.4% and 2.4% of patients with T2DM had their first ischaemic stroke each year. More than a third of them died of CV causes within a year of their stroke. The total 1-year CF after the first ACS or ischaemic stroke is very high and special attention should be focused on improving the situation. Secondary prevention after the hospitalization period should receive an especially high priority.

Men with DM had higher prehospital, 28-day and total 1-year CFs of the first ACS event in all age groups than women with DM. Both men and women had higher 1-year CFs of the first ACS event than their nondiabetic counterparts. The difference was biggest in the younger age group (35–74 years) of women, in whom the 1- year fatality proportion difference was 17.3 percentage points. The CFs decreased significantly in all groups studied and there was no difference in the pace of development between populations with and without DM from 1992 to 2002.

Women with T2DM had somewhat higher CF of the first ischaemic stroke than men with T2DM. Patients with T2DM had a higher CV CF than nondiabetic patients both in the acute phase (1.1–1.3 times higher) and especially during the first year after the acute phase of stroke (1.4–2.2 times higher). The excess 28-day CF caused by T2DM was similar in both genders and in each age group, but the excess CF for the 28-day survivors was highest in the younger age group of women (HR 2.2, 95% CI 1.7–2.7). Persons with DM should have strict goals in the treatment of all CV risks they have.

DM remains a major risk for LEA, although the rate of major amputations has drastically decreased from 1988 to 2002.

Patients with DM have benefited from the prevention of CVDs approximately to the same extent as their nondiabetic counterparts. Yet, their risk of developing CVD remains higher and the prognosis after a CV event is poorer, particularly in long-term prognosis after the acute stage of the event. In addition to the primary prevention, more attention should be focused on the secondary prevention of CV events among patients with DM.

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