Intensified multifactorial intervention in patients with type 2 diabetes and microalbuminuria:

Rationale and effect on late-diabetic complications

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1. INTRODUCTION AND AIM

In the not so distant past, type 2 diabetes mellitus was thought to be a relatively benign condition with relatively minor effect on life expectancy (1). Insights have, however, become deeper. Several epidemiological studies have shown that the risk of cardiovascular mortality is two to three times higher in men with diabetes and three to five times higher in women with diabetes than in people without diabetes (2-6). Cardiovascular disease (coronary heart disease, stroke, and peripheral vascular disease) accounts for about 70% of all deaths in people with diabetes mellitus and all manifestations of cardiovascular disease are also substantially more common in patients with type 2 diabetes than in non-diabetic individuals (7). The age-adjusted prevalence of coronary heart disease in Caucasian adults who have diabetes is about 45% compared to about 25% in individuals without diabetes (8). Similarly, diabetic patients without previous myocardial infarction have as high a risk of myocardial infarction as non-diabetic patients with previous myocardial infarction (9), and life expectancy may on average be reduced by five to ten years (10).

Apart from macrovascular disease as described, diabetic nephropathy, retinopathy and neuropathy, so-called microvascular diseases, constitute a major problem in patients with type 2 diabetes mellitus. The range of reported prevalence of diabetic nephropathy defined as macroalbuminuria is wide. In clinically based cohorts (11-13) or cohorts in primary health care centres (14; 15) the prevalence of macroalbuminuria is around 7%. In contrast, Fabre et al (1) reported proteinuria above 500 mg per 24 hours in as many as 16% of type 2 diabetic patients aged 42 to 92 years attending a Swiss outpatient clinic, and a cross-sectional study from Hvidøre in Denmark in 549 type 2 diabetic patients with a mean age of 59 years found a prevalence of macroalbuminuria above 300 mg per 24 hours in 14% of cases (16). The prevalence of macroalbuminuria in other population based Caucasian cohorts is around 10% (17; 18). Longitudinal population cohorts have revealed a cumulative incidence of proteinuria of 25-50% after 20 years of type 2 diabetes (19-22), and it is estimated that 0.5% of all type 2 diabetic patients in the United States will progress to end stage renal disease (ESRD) during a 10 year period (23).

The prevalence of reported retinopathy also differs in various settings. In the United Kingdom Prospective Diabetes Study (UKPDS) 37% of patients with newly diagnosed type 2 diabetes included in the study had retinopathy at the time of enrolment when retinopathy was defined as microaneurysms being the least severe lesion (24). In contrast, only 5% of 1136 Danish patients with newly diagnosed type 2 diabetes participating in a randomised controlled trial of structured personal care of type 2 diabetes had retinopathy using a similar definition (25). One explanation for this discrepancy could be the time passed from elevated levels of plasma glucose occurs until the disease is diagnosed, since it is well known, that there in most cases is a time gap from the onset of type 2 diabetes of four to seven years until clinical diagnosis (26). Another explanation is the presence of other risk factors such as e.g. elevated levels of urinary albumin excretion rate (UAER). In order to obtain a true picture of the prevalence patients must be examined in a cross-sectional study including all type 2 diabetic patients in a given region. Such a study was performed at a primary health care station in Sweden providing health care for 10,300 people (27). Ninety-nine percent of all diagnosed type 2 diabetic patients aged less than 70 years in the region of Kisa were identified and examined (n=123) giving a prevalence of retinopathy of 27%. Other studies in selected patients attending hospital clinics have revealed much higher prevalences of diabetic nephropathy in the order of more than 50% (14).

Compared to the vast amount of papers on diabetic nephropathy, the literature about the prevalence of diabetic neuropathy in type 2 diabetes is sparse. One of the main reasons for this has been the lack of recommendations of standardised measures in diabetic neuropathy. A consensus development conference chaired by the American Diabetes Association in 1992 aimed at describing a series of tests with evidence of their validity as well as recommendations of specific guidelines for their application giving researchers standardised tools for examining this complication (28). As seen for both diabetic nephropathy and retinopathy there are large variations in the percentage of type 2 diabetic patients suffering from diabetic neuropathy using validated methods depending on the characteristics of the study population. Peripheral neuropathy was present in 19% of the Danish patients in primary care with newly diagnosed type 2 diabetes mentioned before (25) whereas the prevalence is higher at about 35% in cross-sectional studies of patients attending diabetes clinics (29-31). The prevalence of autonomic neuropathy has also shown great variations probably depending on different methods and varying populations studied. One study found parasympathetic neuropathy in 5% of patients at diagnosis and 65% after 10 years of follow-up (32), while in a Danish study in 110 type 2 diabetic patients 63% of patients with diabetic nephropathy had autonomic neuropathy compared to 15% of patients with normoalbuminuria (33).

Until recently the treatment of type 2 diabetes has been empirical and many physicians questioned whether the evidence based treatment of risk factors for micro- and macroangiopathy in type 1 diabetes or in the non-diabetic population could be extended to include type 2 diabetic patients. In recent years, however, results have been published from a number of randomised intervention trials in patients with type 2 diabetes, in which either the effect of treating each single modifiable risk factor or the effect of concurrent intervention against a number of known modifiable risk factors has been investigated.

The aim of the present review is to discuss our present knowledge of the effect of both lifestyle intervention and drug treatment in the prevention of micro- and macroangiopathy in type 2 diabetic patients at high risk for poor outcome, i.e. patients with microalbuminuria or known cardiovascular disease, with emphasis on the multifaceted approach of polypharmacy in combination with behaviour modification. Obviously, problems associated to the different treatments, i.e. side effects and concordance problems will also be considered.

2. SUBJECTS

2.1 DIAGNOSING TYPE 2 DIABETES MELLITUS

In our studies the diagnosis of type 2 diabetes mellitus was based on both clinical and biochemical evaluation of patients as suggested by Hother-Nielsen et al (34). Patients were classified as having type 2 diabetes mellitus according to the following criteria: 1) onset of diabetes after the age of 40; 2) a glucagon-stimulated serum C-peptide value ≥600 pmol/l (35-37).

2.2 MICROALBUMINURIA

As mentioned previously microalbuminuria defined as a persistently elevated UAER in the range 30 to 300 mg per 24 hour is a risk factor for both micro- and macrovascular late diabetic complications (38). Therefore, we chose to examine microalbuminuric type 2 diabetic patients in order to have a well defined study cohort. However, It should be mentioned that microalbuminuria in patients with type 2 diabetes may not be as homogeneous as expected. First, since microalbuminuria at baseline was determined while a large amount of patients were already treated with antihypertensive medication, we may have included some patients with "masked" nephropathy since, as it will be discussed in later sections, antihypertensive treatment lowers UAER. Second, renal structural lesions in patients with type 2 diabetes and microalbuminuria may be quite heterogeneous as suggested by Fioretto et al (39). In this study kidney biopsies from 34 microalbuminuric, unselected type 2 diabetic patients were examined. Thirty percent of patients had normal or near normal renal structure, 30% had "typical" lesions characteristic for diabetic nephropathy (glomerular, tubulo-interstitial and arteriolar changes occurring in parallel) while 40% had "atypical" patterns of injury, with absent or only mild diabetic glomerular changes and concomitant disproportionately severe renal structural changes, which included tubular atrophy, tubular basement membrane thickening, interstitial fibrosis, advanced glomerular hyalinosis and global glomerular sclerosis. While none of the patients in the latter group had any definable non-diabetic renal disease, some of these lesions may be caused by renal ischaemia as a result of atherosclerotic renal artery stenosis or cholesterol microembolism (40).

As it will be described in later sections microalbuminuria is a strong risk factor for both cardiovascular disease as well as late-diabetic microvscular complications, thus the inclusion criterion of microalbuminuria in the Steno-2 ensured a high risk population for these complications.

2.3 ETHNIC ORIGIN

Large variations in the prevalence of type 2 diabetes and its complications have been described among patients of different ethnic origin (41-43). To minimise heterogeneity by the potential confounding effect of race we therefore in the present studies chose only to include patients who were Danish Caucasians by self-report.

2.4 COMPOSITION AND SAMPLING OF THE STUDY POPULATION

The overall purpose of the patient selection was to study a group of type 2 diabetic patients with well defined characteristics as mentioned above. All patients were recruited from Steno Diabetes Center. For the multifactorial intervention study (44-47) and epidemiological studies (48; 49) all type 2 diabetic patients aged 40 to 65 years who during 1992 had a UAER of 30 to 300 mg per 24 hour in a single urine sample were eligible (n=315). Thirty-seven patients refused to participate, 104 patients did not fulfil our criteria for microalbuminuria, 9 patients had a stimulated serum C-peptide level below 600 pmol/l and 5 were excluded of other causes giving a total of 160 patients who with concealed randomisation were divided into two treatment groups in an open, parallel study comparing intensified to conventional multifactorial intervention. Two other studies were carried out as randomised, double-blind, cross-over trials (50; 51). In the vitamin trial (50) 37 consecutive type 2 diabetic patients with microalbuminuria according to definition were eligible. Since treatment with ACE inhibitors were withdrawn eight weeks before treatment with vitamin C and E or placebo patients with prior myocardial infarction or congestive heart failure were excluded from the study (n=4) and three refused to participate giving a total of 30 patients who were randomised. Finally, one patient withdrew during treatment pause, but before active/placebo treatment was initiated. In the aspirin trial treatment with ACE inhibitors was also stopped eight weeks before the first treatment phase and similar exclusion criteria as in the vitamin trial were applied (51). Furthermore, a history of stroke or transitory cerebral ischaemia, peptic ulcer disease, allergy to aspirin and use of cyclooxygenase inhibitors were exclusion criteria. Thirty-one patients out of a total of 43 eligible patients were randomised (two patients refused, four had prior myocardial infarction, two had prior cerebral thrombosis, three used cyclooxygenase inhibitors, and one had a gastrointestinal ulcer). All randomised patients completed this study.

3. STUDY DESIGN

In the two randomised, cross-over trials (50; 51) we used a classical prospective, double-blinded, placebo-controlled study design comparing active treatment to placebo, thus giving an exact effect of the applied single intervention on predefined endpoints. However, in the multifactorial intervention study we chose a newer design called the Prospective Randomised Open Blinded Endpoint (PROBE) study design (52). This design uses a strict randomisation procedure to allocate patients to different treatment regimens. Continuous follow-up and treatment of patients are conducted in an open way that adheres to accepted clinical principles and medical practice. Strictly defined endpoints are blinded during the handling procedure allowing unbiased comparison of therapies and evaluation of the study results. The similarity between a PROBE study and regular clinical practice should make the results obtained in a PROBE trial much more applicable to the practical management of patients. The PROBE design has primarily been used in studies examining the effect of various blood pressure lowering drugs (53-55). Since positive effects of lowering blood pressure have been established, ethical issues prohibit the use of a pure placebo arm in these studies.

The usefulness of the PROBE design was demonstrated in a meta-analysis comparing three PROBE designed trials and two double-blind, placebo-controlled trials examining the impact of angiotensin II receptor blockers on ambulatory blood pressure (56). The analysis had approximately 90% statistical power to show equivalence between the two design types ruling out differences of ≥3 mm Hg in systolic blood pressure and ≥2 mm Hg in diastolic blood pressure. A difference of 0.2 mmHg was found (95% confidence interval -1.1 to 1.5) thus supporting the validity of the PROBE design.

The main advantage with the double-blind trial design is that investigator bias is avoided since the investigator will not be able to identify the treatment regimens during the trial. The possibility of investigator bias is a clear drawback of the PROBE design and as a consequence measures were taken to minimise such bias as much as possible in the multifactorial intervention trial. Strictly defined endpoints were blinded during the handling procedure by the endpoint committee; analysing of biochemical variables and collection of clinical and anthropometrical data were performed by laboratory technicians blinded for treatment allocation, and all data were entered in a database by secretaries also unaware of treatment allocation.

4. METHODS

4.1 KIDNEY FUNCTION

4.1.1 Glomerular filtration rate (GFR)

GFR was estimated in the supine position from plasma clearance following a single bolus injection of 3.7 MBq ^{51}Cr-labelled edetic acid in the morning by determining the radioactivity in venous blood samples taken from the other arm 180, 200, 220 and 240 min-

utes after the injection with appropriate corrections and standardisation for the patient's surface area (57-59).

When progression in any chronic kidney disease is evaluated development of ESDR is the ultimate endpoint. Since it takes several years to reach ESRD clinical trials in progressive kidney disease often requires other endpoints. The rate of decline in GFR has been approved as an endpoint by the Food and Drug Administration (USA). The rate of decline in GFR was only calculated for patients completing follow-up (44; 46) or was calculated as the difference between first and last GFR determination in all participating patients (51).

4.1.2 Urinary albumin excretion rate

Due to large day to day variation in UAER (60) three 24-hour urinary collections were performed at each designated time point in all our studies. Indeed six 24-hour collections were used to confirm microalbuminuria at baseline in two studies (44; 46). Timed urinary collections were used as it is widely accepted as the most accurate method for determination of UAER (61). The urinary albumin concentration was determined by an immunoassay method (62). Normoalbuminuria was defined as UAER <30 mg per 24 hour, microalbuminuria as UAER 30-300 mg per 24 hour, and macroalbuminuria as UAER >300 mg per 24 hour as defined at a consensus conference (63). The fractional clearance of albumin was calculated by dividing the clearance of albumin (calculated as UV/P, where U is urine albumin concentration (mg/l), V is urine flow (l/24 h), and P is plasma albumin concentration (g/l)) with the simultaneous measured GFR to correct albumin excretion for changes in plasma albumin concentration and in GFR (51).

4.2 ENDOTHELIAL DYSFUNCTION

Endothelial function was evaluated by determining the transcapillary escape rate of albumin (TER_{alb}) in one study (51) and with measurement of the serum concentration of von Willebrand factor (vWF) after an overnight fast (48).

4.2.1 Transcapillary escape rate (TER_{alb})

TER_{alb} is defined as the fraction of the intravascular mass of albumin that passes to the extravascular space per unit of time (percent per hour). It is determined as the rate constant of the practically monoexponential decrease in plasma radioactivity over the first 60 minutes following injection of tracer albumin as calculated by the least squares method as described (64).

4.2.2 Von Willebrand factor

Von Willebrand factor is a high molecular weight glycoprotein synthesised mainly by the endothelial cells and acts as a non-specific marker of endothelial dysfunction (65; 66). The plasma concentration of vWF was measured by microenzyme linked immunoadsorbent assay as described by Ingerslev (67). A close agreement between plasma and serum levels of vWF has been described (68).

4.3 LABORATORY ASSAYS

4.3.1 Glycaemic regulation

Glycosylated haemoglobin A_{1c} was determined by ion-exchange high-performance liquid chromatography (HPLC) (Bio-Rad VARIANT, California, USA) and the non-diabetic reference range in our laboratory was 4.1-6.4%. Blood glucose was measured by a glucose oxidase method.

4.3.2 Lipid profiles

Venous blood samples were drawn after a 12 hour fast. Serum total cholesterol and serum high density lipoprotein (HDL)-cholesterol were measured by chromatography and serum triglycerides were measured by colorimetry. Serum low density lipoprotein (LDL)-cholesterol was calculated by the Friedewald formula (69) in patients with a serum triglyceride concentration lower than 5 mmol/l.

4.3.3 Pancreatic β-cell function

Serum C-peptide concentration was measured by radioimmunoassay (RIA) (70) in the fasting state and 6 minutes after intravenous injection of 1 mg glucagons to measure residual β-cell function (35).

4.3.4 Vitamin E and C

Plasma α-tocopherol, ascorbic acid and its metabolite dihydroascorbic acid were measured by HPLC (71; 72).

4.3.5 Plasma NT-proBrain Natriuretic Peptide(NT-proBNP)

After the patients had been at rest for at least 20 minutes in the supine position, blood samples (EDTA plasma) for analysis of plasma NT-proBNP were collected, centrifuged and plasma stored at –80°C until analysis. Plasma concentrations of NT-proBNP were measured by a sandwich immunoassay on an Elecsys 2010 (Roche Diagnostics, Germany). The analytical range extends from 5 to 35 000 pg/ml, and the total coefficient of variation is <0.061 in pooled human plasma samples (73). To convert from pg/ml to pmol/l multiply by 0.118.

4.4 ARTERIAL BLOOD PRESSURE

Arterial blood pressure was measured with a Hawksley random zero sphygmomanometer (Hawksley & Sons Ltd, Lancing, Sussex, UK) and by the use of an automatic, oscillometric manometer (Takeda Medical UA-751, Tokyo, Japan).

Arterial blood pressure was after an overnight fast measured twice on both arms in the supine position with the random zero device after 20 minutes rest by a laboratory technician unaware of both treatment allocation and actual treatment and the average of these four measurements was used. Cuff size 25 × 12 cm was used if the upper arm circumference was below 35 cm, and cuff size 30 × 15 cm was used if upper arm circumference was equal to or above 35 cm. Diastolic blood pressure was recorded at the disappearance of Kortokoff sounds (phase 5). Patients did not take any medication before blood pressure measurements. The Hawksley random zero sphygmomanometer was used to exclude bias in the readings as compared to a simple mercury manometer. Yet, the Hawksley apparatus has been criticised for being inaccurate, especially in the measurement of systolic blood pressure, where an underestimation of 2 to 4 mm Hg was found (74; 75).

The automated Takeda UA-751 manometer was used for determination of the reference arterial blood pressure in the systolic arm-toe gradient and for the blood pressure measurements for orthostatic hypotension. An appropriate cuff size as mentioned above was used. The Takeda UA-751 gives difference in systolic blood pressure of -0.11 +/- 5.6 mm Hg (mean +/- SD) and in diastolic blood pressure of 0.31 +/- 5.5 mm Hg as compared to a mercury sphygmomanometer (76).

4.5 RETINOPATHY

Two mydriatic 60-degree fundus photographs were taken on 35 mm colour transparency film one covering the macula-temporal part of the retina and one covering the optic disc and nasal part of the retina. The photographs were graded according to the EURODIAB six-level grading scale (77) by two independent graders masked for treatment allocation (44; 46). Any presence of maculopathy was determined by evaluation of a stereo-set of photographs of the macula region and data were drawn from the files of the eye clinic at Steno Diabetes Center. The evaluation of any maculopathy was masked for treatment allocation and done by graders independent from our studies at the Steno Diabetes Center. Visual acuity was measured with dilated pupils by a Nikon NR-7000 autorefractor with a cut off upper limit of 1.0 refracted visual acuity. Blindness was defined by WHO criteria as a visual acuity equal to or less than 0.1.

4.6 DIABETIC NEUROPATHY

4.6.1 Autonomic nervous function

The beat-to-beat variation is a simple bedside test that mainly evalu-

ates cardiac vagal function. The interpretation of the test results as originally proposed by Hilsted et al (78) (abolished <4 beats/min, impaired 5-15 beats/min and normal >15 beats/min) has been challenged, since it has been shown that beat-to-beat variation decreases with older age (79-81). Indeed the overestimation of the prevalence of impaired cardiac vagal function in middle-aged type 2 diabetic patients by the use of normal values derived from young healthy subjects by applying the original criteria was obvious in a cross-sectional study by Nielsen et al (33) since the prevalence of impaired and abolished beat-to-beat variation was very high in the non-diabetic control group. As a consequence we used values obtained from this non-diabetic control group as normal values (abolished <4 beats/min, impaired 4-6 beats/min and normal >6 beats/min). We used 3 lead electrocardiogram (ECG) monitoring with a paper velocity of 25 mm/second. Beat-to-beat variation was calculated as the difference between maximal and minimal heart rate during in- and expiratory phase. The mean value obtained from 5 in- and expiratory cycles was used.

Autonomic sympathetic nervous function was evaluated by orthostatic blood pressure test. Arterial blood pressure was measured twice in the right arm after 30 minutes rest in the supine position. Systolic blood pressure was recorded at 0.5, 1.5, 3, 5 and 7 minutes after rising to an upright position. Orthostatic hypotension was diagnosed if the maximal fall in systolic blood pressure exceeded 25 mm Hg in any of the measurements (82).

4.6.2 Peripheral nervous function

Measurement of the vibration threshold with the use of a biothesiometer was used to evaluate peripheral neuropathy. We used an age-adjusted scale as described by Bloom et al (83). Testing was standardised so that the tactor was held in firm contact but with minimal pressure against the skin. The plantar aspect of the great toe opposite the nail bed was used. Although stockings and thin socks did not alter the thresholds in the reference population (83) measurements in our studies were obtained on the bare foot. In case of amputation of the first toe, measurements were done in the adjacent toe.

4.6.3 Are the methods used in the evaluation of neuropathy reliable?

Diabetic polyneuropathy presents with a wide range of symptoms reflecting the broad range of nerve fibre types involved. According to the American Diabetes Association and the Rochester Diabetic Neuropathy Study evaluations for diagnosis and staging of diabetic polyneuropathy should include assessment of a) neuropathic symptoms, b) neuropathic deficits, c) nerve conduction, d) quantitative sensory examination, and e) quantitative autonomic examination (84; 85). The protocol applied in the Steno-2 study does not fulfil all of these criteria. Whereas the methods used for measurement of autonomic nerve function (beat to beat variation and orthostatic hypotension test) are fully validated and acceptable according to present consensus, thus fulfilling criterion e), this is not the case for peripheral nerve function. Measurement of vibration threshold with a biothesiometer as described is a simple bedside test for evaluating peripheral nerve function with a high retest reliability making it suitable for follow-up studies (86). However, it only studies the unmyelinised C-fibre qualities, whereas the fastest and more important myelinised A-fibres are not assessed. Since sensory examination in criterion d) requires both examination of hypaesthesia, hypalgesia, and vibration threshold, this criterion is only partly fulfilled. Criterion a), b), and c) have not been met. Our finding of a lack of effect of intensified multifactorial intervention on peripheral nerve function in microalbuminuric patients with type 2 diabetes both after four and eight years of follow-up should be seen in the light of this weakness in our methods for measurement of peripheral neuropathy (44; 46). Also, it should be underlined that development or progression of diabetic neuropathy was a secondary and tertiary endpoint, respectively.

4.7 CARDIOVASCULAR DISEASE

Past and present symptoms of cardiovascular disease were registered according to the World Health Organization cardiovascular questionnaire (87).

A 12-lead resting ECG was recorded. The ECG was coded independently by two trained, masked observers using the Minnesota Rating Scale (88). Minnesota codes 1.1-1.3, 4.1-4.4, 5.1-5.8 and 7.1 were taken as sign of cardiac ischaemia.

Exercise stress test was done with a bicycle ergometer (Kivex, Copenhagen, Denmark) beginning at 25 W and increasing the work load with 25 W every second minute. All electrocardiograms were evaluated by two independent, masked graders. Ischaemia was present if ST-depression was greater than 1 mm in any lead.

Digital systolic blood pressure in the lower limb was measured in the first toe using a strain gauge technique (89).

An independent, masked endpoint committee consisting of 2 specialists in cardiology and one specialist in diabetology evaluated all cases and classified cardiovascular events into the following categories: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, amputations, invasive cardiovascular procedures, and peripheral vascular procedures (Appendix 1).

The role of plasma NT-proBNP as a risk factor for cardiovascular disease and heart failure was also studied in the Steno-2 cohort (49). A secondary endpoint comprising cardiovascular mortality as defined above as well as heart failure was examined. Heart failure was defined as admission for heart failure documented by discharge letters.

5. LIFESTYLE AND DRUG INTERVENTIONS IN THE STENO-2 STUDY

5.1 LIFESTYLE EDUCATION

The underlying theories and the practical approach to lifestyle education about diet, exercise and smoking in the Steno-2 study are discussed in detail in one of the reports from the study (45).

5.2 DRUG THERAPY

The following is a summary of the drug treatment strategy in the intensive therapy group in the Steno-2 study (44; 46). Treatment was target driven according to the overall treatment goals set in the study protocol, yet in order to increase adherence to the various drug treatments, we chose to use a stepwise implementation based on individual risk assessment and individualised intermediate goals.

5.2.1 Hyperglycaemia

The goal for blood glucose was a glycosylated haemoglobin A_{1c} (HbA_{1c}) below 6.5%. If patients were unable to maintain HbA_{1c} values below 6.5 percent on diet and increased physical activity alone after 3 months, treatment with oral hypoglycaemic agents was started. As the initial step overweight patients (body mass index (BMI) >25 kg/m^2) received metformin to a maximum of 1 g twice daily; lean patients, or overweight patients with contraindications to metformin, received gliclazide to a maximum of 160 mg twice daily. As the second step metformin was added to lean and gliclazide to overweight patients if hyperglycaemia was not controlled. If HbA_{1c} was above 7.0 percent despite maximum doses of oral agents the addition of neutral protamine Hagedorn (NPH) insulin at bedtime was recommended. When insulin was started lean patients stopped metformin treatment and overweight patients stopped gliclazide unless this was the only oral hypoglycaemic agent given. The insulin dose was adjusted by the morning fasting blood glucose concentration (90). If the average fasting blood glucose exceeded 7 mmol/l during a three day period, patients increased the evening NPH insulin dose with four units until the fasting blood glucose had reached target. If the daily insulin dose exceeded 80 IU or there was no decrease in HbA_{1c} patients were switched to insulin regimens with NPH insulin given two times a day or short acting insulin to main meals and NPH insulin at bedtime. There was no upper limit for the daily insulin dose.

5.2.2 Hypertension

During the first six years of the study the goal for blood pressure was 140/85 mm Hg, but since newer and stricter guidelines were applied to the conventional group during the last two years of the study, the goal in the intensive therapy group was intensified to 130/80 mm Hg during this period. Our first line strategy was blockade of the renin-angiotensin system with the angiotensin converting enzyme inhibitor captopril 50 mg twice daily. In case of side effects the angiotensin II receptor antagonist losartan 50 mg twice daily was given. During the last two years of the study we had the possibility of combining the two drugs (91). If goals were not met the second step was addition of diuretics. Depending on whether patients had oedema or not furosemide with an initial dose of 40 mg daily or bendroflumethiazide 5 mg administered once daily was prescribed. The third step was addition of the long-acting dihydropyridine calcium antagonist amlodipine 10 mg given once daily. The beta-blocker metoprolol with a maximum dose of 200 mg per day was the fourth step in treating uncontrolled hypertension in the intensive therapy group.

5.2.3 Dyslipidaemia

The goal for treatment of dyslipidaemia was based on fasting serum levels of total cholesterol and triglycerides. The goal for fasting serum total cholesterol was 5.0 mmol/l during the first six years of the study with a tighter goal of 4.5 mmol/l during the last two years. The goal for fasting serum triglycerides was 1.7 mmol/l throughout the entire study period. Initially fluvastatin was used, but since atorvastatin became available in Denmark during the last four years of the study this drug was used. The dose was titrated based on fasting serum total cholesterol levels to a maximum of atorvastatin 40 mg per day. In case of an elevated fasting serum triglyceride level above 4.0 mmol/l despite treatment with a statin, the fibrate gemfibrozil in a maximal dose of 600 mg twice daily was used in combination with the statin.

5.2.4 Microalbuminuria

All 160 patients included in the Steno-2 study had microalbuminuria. Based on the early findings from the study by Ravid et al (92), where beneficial effects on kidney function were seen in normotensive patients with type 2 diabetes, all patients in the intensive therapy arm were given ACE inhibition with captopril 50 mg twice daily irrespective of blood pressure level. In case of side effects the angiotensin II receptor antagonist losartan 50 mg twice daily was prescribed.

5.2.5 Acetylsalicylic acid

The use of low-dose acetylsalicylic acid (ASA) was quite extensive throughout the entire study period. During the first six years ASA 150 mg daily was given as *secondary* prevention to patients with a history of a) transitory ischaemic attack, b) stroke, c) myocardial infarction, d) signs of ischaemic heart disease, and e) systolic toe/brachial blood pressure index below 0.67. During the last two years of the study ASA 150 mg daily was recommended as primary prevention to all patients in the intensive therapy group unless contraindications were present.

5.2.6 Vitamins

As discussed in a later chapter the use of vitamins and minerals in the prevention and treatment of late diabetic complications is controversial. During the first four years of the study patients were recommended a tablet consisting of vitamin C 250 mg and vitamin E (d-α-tochopherol) 100 mg. The recommended dose was one tablet daily for non-smokers and five daily tablets for smokers. Furthermore, one multivitamin tablet was recommended to all patients in the intensive therapy group. During the last four years of the study the daily recommendations also consisted of chromium piccolinate 100 µg and folic acid 400 µg daily.

6. RISK FACTORS FOR LATE DIABETIC COMPLICATIONS IN TYPE 2 DIABETES

Epidemiological studies have investigated the effect of several risk factors for development and progression of macro- as well as microvascular complications in patients with type 2 diabetes. Since identification of modifiable risk factors is the basis of reducing or preventing complications the following paragraphs discuss the associations of selected risk factors and complications from epidemiological studies. Later chapters will discus the results from studies targeting modifiable risk factors as monofactorial intervention or as part of a multifactorial treatment strategy.

6.1 RISK FACTORS FOR CARDIOVASCULAR DISEASE IN TYPE 2 DIABETES

Recently, a major case-control study (the INTERHEART study) investigated the effect of potentially modifiable risk factors associated with myocardial infarction in almost 30,000 subjects from 52 countries (93). The conclusion was that current smoking, lipid abnormalities, hypertension, abdominal obesity, psychosocial factors, and diabetes were associated with an increased risk of myocardial infarction, while daily consumption of fruits and vegetables, regular alcohol consumption, and regular physical activity decreased the risk. These nine modifiable risk factors accounted for more than 90% of the risk for a myocardial infarction in the population. A similar large-scale study has not been performed in patients with type 2 diabetes, but several risk factors have been identified.

6.1.1 The classic risk factors

Data from prospective observational studies indicate that the major cardiovascular risk factors in the non-diabetic population, that is smoking, hypertension and dyslipidaemia, also operate in diabetic subjects (2; 94). Also genetic factors are important since the prevalence of cardiovascular disease (CVD) is influenced by the population itself (95). In the Multiple Risk Factor Intervention Trial (MRFIT) (2) more than 5,000 men with type 2 diabetes and 340,000 non-diabetic men were followed for 12 years. The risk for cardiovascular mortality increased significantly with the number of risk factors (systolic blood pressure, total serum cholesterol, and smoking) in both the diabetic and non-diabetic men, but the risk of cardiovascular death was two to three-fold increased in the diabetic population for each combination of risk factors. Increased systolic blood pressure is more common in type 2 diabetes than in the general population (3; 96). In the UKPDS observational study a 10 mm Hg decrease in updated mean systolic blood pressure during treatment was associated with a significant 11% relative reduction in the risk for myocardial infarction, a 19% relative reduction in the risk for stroke, and a 15% relative reduction in the risk for diabetes related death (97). It should, however be noted, that the strongest risk factor for CVD in the UKPDS was dyslipidaemia with estimated hazard ratios for the upper third relative to the lower third of 2.26 for fasting serum LDL-cholesterol, and 0.55 for HDL-cholesterol (94). In the same study, current smoking was of borderline significance only. Since the classic risk factors do not explain all of the excess cardiovascular mortality in patients with diabetes other risk factors must be of importance (98; 99).

6.1.2 Hyperglycaemia

Several prospective studies have shown that in type 2 diabetes hyperglycaemia increases the risk for myocardial infarction (94; 100; 101), stroke (102), macrovascular mortality (103-105), and all-cause mortality (103; 106-109). It should here be mentioned that many earlier studies have been hampered by the lack of valid estimates of long-term glycaemic regulation. Measurement of glycosylated haemoglobin concentrations yield such estimates, however the method has only been available for the last 20 years and as a consequence, many previous studies have been based on measurements of fasting

or random plasma glucose levels, which are less accurate in estimating long-term glycaemic regulation.

6.1.3 Hyperinsulinaemia

Hyperinsulinaemia has generally been considered a marker of insulin resistance, i.e. a decrease in the effect of insulin to stimulate glucose uptake at a given serum insulin concentration. Since high serum insulin concentrations in animal studies stimulate cholesterol synthesis and binding of LDL-cholesterol to smooth muscle cells and macrophages in the arterial wall (110) a causative link between elevated levels of serum insulin and the risk for cardiovascular disease may exist. Such an association has been found both in non-diabetic men (111; 112) and in type 2 diabetic patients (113). In 1988 Reaven introduced the term Syndrome X or the metabolic syndrome and suggested that insulin resistance and compensatory hyperinsulinaemia may underlie the clustering of cardiovascular risk factors seen in type 2 diabetes as a possible mechanism for the increased risk for CVD in these patients (114). In a recent study from Finland the clustering of a high BMI, high fasting serum triglyceride concentration, low fasting serum HDL cholesterol and hyperinsulinaemia predicted cardiovascular mortality in type 2 diabetic patients who were not treated with insulin (115).

6.1.4 Dyslipidaemia

It has long been known that more than half of patients with newly diagnosed type 2 diabetes have dyslipidaemia (116). The typical pattern is elevated levels of fasting serum triglycerides, decreased levels of fasting serum HDL-cholesterol, a predominance of small dense LDL particles, and exaggerated postprandial lipidaemia (117). Epidemiological studies have established a direct proportional relation between the fasting serum concentrations of total-cholesterol or triglyceride and the risk for ischaemic heart disease in type 2 diabetes (2). The importance of dyslipidaemia in predicting cardiovascular disease in patients with type 2 diabetes is also seen from the UKPDS, where the most important predictor for CVD during a nine year period was increased fasting serum LDL-cholesterol followed by decreased fasting serum HDL-cholesterol concentration, as mentioned previously (94).

6.1.5 Microalbuminuria

In 1984 both Mogensen (118) and Jarret (119) reported independently that microalbuminuria predicted all-cause mortality in type 2 diabetes. These findings have later been found also to extend to CVD morbidity in both men and women (120). Thus, an extensive review of the literature carried out by Dinneen and Gerstein (38) has confirmed the strong association between microalbuminuria and cardiovascular mortality in type 2 diabetes. Interestingly, this association between high levels of UAER and cardiovascular disease and mortality has been shown also to extend to the non-diabetic population, even within the normal range of UAER as is also the case for patients with type 2 diabetes (121-124). Why the development of microalbuminuria, in itself reflecting a trivial loss of albumin, should herald such serious and anatomically far reaching consequences is not understood. In an attempt to explain this, Deckert et al have put forward the hypothesis that increased UAER loss merely reflects a glomerular manifestation of an otherwise generalised (but less clinically visible) vascular hyperpermeability state (125). Additional plausible explanations might be the association between microalbuminuria and insulin resistance and the components of the insulin resistance syndrome in type 2 diabetes (126; 127).

6.1.6 Hypercoagulation and endothelial dysfunction

An imbalance in the haemostatic system due to hypercoagulability or impaired fibrinolytic function may favour the development of vascular damage. Plasminogen activator inhibitor type 1 (PAI-1) is a potent inhibitor of fibrinolysis, and increased plasma levels of PAI-1 have been demonstrated in patients with coronary artery stenosis or after acute myocardial infarction (128). Epidemiological studies have suggested links between plasma PAI-1 levels and the components of the metabolic syndrome (129). Fibrinogen is another player in the coagulation system and raised circulating concentrations favour coagulation, increase platelet activation and adherence to the endothelium, and have been associated with CVD in the general population (130). In type 2 diabetes a similar association has been shown with circulating fibrinogen levels increasing with age, hyperglycaemia, smoking, hypertension and other components of the metabolic syndrome (131). Elevated levels of plasma von Willebrand factor have also been associated with increased cardiovascular mortality in type 2 diabetes (104) and some prospective studies even suggest that the role of microalbuminuria in predicting CVD in type 2 diabetic patients is largely influenced by the absence or presence of endothelial dysfunction as measured by elevated plasma levels of vWF (132; 133). We also examined this concept in a post-hoc follow-up study lasting for an average of 3.8 years in the 160 microalbuminuric patients participating in the Steno-2 study (48). Patients were divided into two groups according to plasma vWF levels below or above the median at baseline. Although the odds ratio for cardiovascular disease was 1.11 with elevated plasma vWF this difference was not significant in our setting.

6.1.7 N-terminal-proBrain Natriuretic Peptide

Brain natriuretic peptide (BNP) is synthesised by cardiocytes as a response to increased cardiac wall stress and mediates natriuresis, diuresis and vasodilatation (134). BNP is synthesized as a prohormone which is cleaved into BNP and N-terminal proBNP (NT-proBNP), the latter being more stable in vitro with a longer half-life. The role of BNP as a prognostic risk marker for CVD has been investigated in patients with chronic heart failure and acute myocardial infarction showing increased risk for future CVD morbidity or mortality with elevated plasma levels of BNP. Measurement of plasma NT-proBNP seems to provide the same information as plasma BNP (135). The role of plasma NT-proBNP as a risk marker for CVD was examined in the Steno-2 cohort (49). In this study sample the range of fasting plasma levels of NT-proBNP at baseline was 5.0 (lowest detectable value) to 1290.0 pg/ml with a median value of 33.5 pg/ml. Interestingly, the level of plasma NT-proBNP was low in the type 2 diabetic patients with microalbuminuria included in the Steno-2 Study, thereby expanding the use of NT-proBNP as a risk marker for future CVD to levels seen in the general population (136). Plasma NT-proBNP levels above the median were significantly correlated with an increased risk of CVD as defined in the Steno-2 study (Hazard ratio 4.4 (95% confidence interval 2.3-8.4), ($p<0.0001$)) as well as a secondary combined endpoint of cardiovascular mortality and hospitalization for heart failure (Hazard ratio 5.8 (2.0-16.9), $p=0.001$). The association between elevated levels of plasma NT-proBNP and prognostic outcomes was also seen when each of the two original treatment groups (intensive therapy or conventional therapy) was analysed separately (49).

6.1.8 Other risk factors

Although lack of physical activity predicts CVD in non-diabetic individuals (93; 137), data in diabetic patients are limited. Yet, a low level of physical activity has been associated with increased risk for CVD in men with type 2 diabetes (138). Obesity, a very common characteristic of type 2 diabetes, has not independently been associated with CVD in diabetic patients (139; 140). Still, central obesity predicts CVD in prospective studies independently of overall obesity in men with type 2 diabetes (141).

6.2 RISK FACTORS FOR MICROVASCULAR COMPLICATIONS IN TYPE 2 DIABETES

Several studies have investigated the relationship between putative risk factors and diabetic nephropathy, retinopathy, and neuropathy (17; 19; 42; 142-167). Table 1 gives a brief summary of current

Table 1. Selected risk factors and their association with microangiopathy in patients with type 2 diabetes. Table is based on references (17; 19; 42; 142-167).

Nephropathy		Retinopathy		Neuropathy	
Hyperglycaemia	+	Hyperglycaemia	+	Hyperglycaemia	+
Hypertension	+	Hypertension	+	Hypertension	+
Dyslipidaemia	+	Dyslipidaemia	+/–	Dyslipidaemia	+
Microalbuminuria	+	Microalbuminuria	+	Microalbuminuria	+
Antioxidant state	?	Antioxidant state	?	Antioxidant state	?
Smoking	+	Smoking	–	Smoking	+
Ethnic origin	+	Insulin treatment	?	Overweight	+
Familial clustering	+	Familial clustering	?		

+ Association present; – Association not present; ? Scanty or no relevant information.

knowledge in this area. As seen from this table with selected risk factors many of the risk factors known to have impact on the development of CVD also play an important role in the development of microvascular complications. The associations between hyperglycaemia and both diabetic nephropathy, retinopathy and neuropathy seem quite consistent while evidence is far less convincing for some of the other risk factors.

7. INTERVENTION AGAINST MODIFIABLE RISK FACTORS IN TYPE 2 DIABETES

Until recently the treatment of type 2 diabetes was empirical and many physicians questioned whether the evidence-based treatment of risk factors for micro- and macroangiopathy in type 1 diabetic patients or in the non-diabetic population could be extended to the treatment of type 2 diabetes. In the recent decade, however, results have been published from a number of randomised intervention studies of patients with type 2 diabetes, in which either the effect of treating each individual modifiable risk factor or the effect of concurrent intervention against a number of known modifiable risk factors have been investigated. The interventions can be divided into two major categories, namely lifestyle interventions targeting diet, physical exercise, body weight and composition, and smoking habits with possible changes in several concomitant risk factors and specific pharmacological interventions primarily targeting one specific risk factor at a time.

7.1 LIFESTYLE INTERVENTIONS

7.1.1 Diet intervention

The rationale for diet intervention in type 2 diabetes is obvious. Since dietary intervention in short term trials has been shown to reduce several risk factors for both macro- and microvascular complications it remains a cornerstone in the treatment. The effects of diet intervention is either direct from diet itself or indirect from the effect on weight and body composition. It must, however, be emphasised that the benefits of this kind of intervention in reducing complications has never been proven in randomised long-term studies in type 2 diabetes. The following paragraphs will discuss the effect of changing diet upon different risk factors.

7.1.1.1 Effect on hyperglycaemia

Among many studies examining the blood glucose lowering effect of different diets the UKPDS was by far the largest study in type 2 diabetes. The design of the study gave an excellent chance of evaluating the effect of diet on hyperglycaemia in newly diagnosed patients with type 2 diabetes. In 2595 patients who received intensive nutrition counselling by a dietician HbA_{1c} decreased 1.9% (from 8.9% to 7.0%) during the three months run-in period before randomisation. Sixteen percent of patients had normalised their fasting blood glucose levels (<6 mmol/l) during these three months. One year later, however, less than half of the patients were able to maintain normal fasting blood glucose based on the diet alone despite an average weight loss of 9.4 kg (168). An important question is of course whether this deterioration in glycaemic regulation is caused by lack of adherence to the diet. This is indeed a plausible explanation as seen in a study using a cross-over design encompassing 102 type 2 diabetic patients above the age of 60 years (169). Patients were randomised to immediate or delayed intervention consisting of a ten-session, self-management training program during a three month period given by a multidisciplinary team including a dietician. When the delayed intervention group crossed over to start intervention, HbA_{1c} levels decreased from 7.4% to 6.4% whereas the immediate intervention group had a rebound effect, with HbA_{1c} levels returning to prestudy levels within six months. Similarly, the significant reductions in caloric intake and percentage of energy from fat seen during the intervention period disappeared (169). As a consequence a continuous lifestyle intervention is necessary to obtain long-term changes. The effect of this approach has clearly been demonstrated by our own results from the Steno-2 study, where the increase in intake of carbohydrates, the decrease in the intake of total dietary fat, and the decrease in the intake of saturated fatty acids were significantly larger in the intensive therapy group receiving continuous lifestyle intervention as well as polypharmacy as compared to the conventional group receiving standard care after four and eight years of intervention, respectively (45; 46). This is in accordance with another long-term study in 1,139 patients with newly diagnosed type 2 diabetes from Germany investigating the effect of continuous intensified health education including dietary advice. The group randomised to intensified education had significantly lower values of fasting blood glucose (8.7 versus 9.3 mmol/l) after a five year follow-up period. This reduction was obtained even though a smaller number of patients in the intensive group was treated with oral hypoglycaemic agents (28 versus 47%) (170).

To summarise, hyperglycaemia can be reduced by a proper diet. However, because of progression in the underlying disease an increase in hyperglycaemia will occur in the majority of patients despite maximal adherence to dietary principles.

7.1.1.2 Effect on dyslipidaemia

As with the effect of diet in treating hyperglycaemia, studies have investigated the effect of different diet interventions in the treatment of dyslipidaemia in patients with diabetes. Again it is characteristic for these trials that they are mainly short-term trials and that they have not proven any effect against late diabetic complications. Another important aspect is, that in most studies patients with diabetes only constitutes a subgroup of the examined population, and in many cases insulin treated type 2 diabetic patients have been excluded from the studies. In a substudy from the Dietary Approaches to Stop Hypertension (DASH) trial the effects of a diet rich in fruits, vegetables, and low-fat dairy foods and with reduced saturated and total fat was investigated in 436 patients with hypertension (mainly African American) over an eight week period (171). There is no information of the number of patients with diabetes included. No change in weight were seen during the trial, but patients randomised to the specific diet had significantly lower values of fasting serum total cholesterol (-0.35 mmol/l) and serum LDL-cholesterol (-0.28 mmol/l) but no change in fasting serum triglycerides as compared to patients randomised to the control diet. A larger decrease of 0.09 mmol/l in serum HDL-cholesterol levels was also seen with the specific diet.

In another study, dietary fat restriction and an average weight loss of 6 kg resulted in decreased fasting plasma triglycerides and a modest lowering of plasma LDL-cholesterol in type 2 diabetic patients during a four week period. Only reductions in central obesity was correlated with a less atherogenic lipid profile (172).

In type 2 diabetic patients with mild-to moderate elevations of plasma triglycerides and low plasma HDL-cholesterol, replacing saturated fat with carbohydrate has been shown to result in improvement of fasting plasma LDL-cholesterol with beneficial or neutral effects on fasting plasma triglycerides and plasma HDL-cholesterol (173), although another study found that the improvements in fasting plasma LDL-cholesterol with such a diet was associated with a

30% increase in fasting plasma triglyceride over a 6 week period (174).

Since maximal changes in nutrition typically reduce fasting plasma LDL-cholesterol by 0.4 to 0.65 mmol/l pharmacological therapy is likely to be necessary if LDL-cholesterol exceeds the goal by more than 0.65 mmol/l (175).

7.1.1.3 Effect on hypertension

Nutritional management of hypertension has focused on reducing weight and dietary sodium intake. In a metaanalysis of 11 weight loss trials, the average systolic and diastolic blood pressure reductions per kilogram of weight loss were 2 and 1 mm Hg, respectively (176). None of the studies were done exclusively in diabetic patients. However, there is no reason to believe that differences exist between diabetic and non-diabetic individuals regarding weight reduction and the effect on blood pressure. Similarly, a review of 32 trials covering 2635 subjects concluded that moderate reduction of dietary sodium lowers systolic and diastolic blood pressure (177). The effects were, however, moderate with a reduction of 5 mm Hg systolic and 2 mm Hg diastolic in hypertensive patients and a reduction of 3 mm Hg systolic and 1 mm Hg diastolic in normotensive subjects. A meta-analysis of 56 trials with a randomised allocation to control and dietary sodium intervention groups, monitored by timed urinary sodium excretion reported a comparable result in hypertensive subjects, i.e. a mean decrease in blood pressure per 100 mmol/l decrease in sodium intake per day of 4 mm Hg systolic and 1 mm Hg diastolic (178).

In the randomised DASH trial the effects of a diet rich in fruits, vegetables, and low-fat dairy foods and with reduced saturated and total fat (DASH diet) was investigated in 459 individuals during an eight week period (179). Compared to a traditional American diet the DASH diet lowered systolic and diastolic blood pressure by 6 mm Hg and 3 mm Hg, respectively. In a recent study three levels of sodium intake (150 mmol/day (high), 100 mmol/day (intermediate), and 50 mmol/day(low)) both during a traditional American and during a DASH diet were compared during a 30 day period (180). The DASH diet was associated with a significantly lower systolic blood pressure at each sodium level, and the difference was greater with high sodium levels than with low ones. As compared with the control diet with a high sodium level, the DASH diet with a low sodium level led to a mean systolic blood pressure that was 7.1 mm Hg lower in participants without hypertension, and 11.5 mm Hg lower in participants with hypertension.

In conclusion, there is definite proof that a proper diet can reduce blood pressure in patients with hypertension. Although no large scale studies have been performed in patients with type 2 diabetes, there is no reason to assume that diet intervention would be less effective in this population.

7.1.2 Exercise

The possible benefits of exercise for the patient with type 2 diabetes are substantial since in epidemiological studies positive effects of exercise are seen on several risk factors such as hyperglycaemia, dyslipidaemia, and hypertension. As for diet the effects are mediated either by exercise itself or by changes in weight and body composition. Yet, no randomised studies have documented any effects on macro- or microvascular complications in these patients.

7.1.2.1 Effect on hyperglycaemia

The effect of both acute and chronic exercise on insulin sensitivity has been assessed in intervention studies (181). Thus, a single bout of acute exercise enhances insulin-mediated glucose disposal in patients with type 2 diabetes (182). Improvements in insulin sensitivity is seen 12-48 hours after the exercise bout, but is virtually unmeasureable 3-5 days after the last exercise session stressing the importance of chronic exercise (183). Fortunately, the same study showed that the beneficial effect can rapidly be regained by one single bout of exercise. Current recommendations for exercise in type 2 diabetic patients are three to seven physical sessions spaced throughout the week. The intensity should be moderate to strong, and the duration from 15 to 60 minutes at training intensity. Both high and low pulse training should be practiced (181).

7.1.2.2 Effect on dyslipidaemia

Intervention studies in patients with dyslipidaemia have shown that unfavourable serum lipid and lipoprotein profiles respond favourably to exercise training (181). According to epidemiological studies, physically active individuals have higher fasting serum levels of HDL-cholesterol and lower levels of triglycerides and LDL-cholesterol compared to sedentary subjects. It is generally believed that this also applies to patients with type 2 diabetes.

7.1.2.3 Effect on hypertension

A meta-analysis of 25 studies (both intervention and epidemiological) examining the antihypertensive effects of exercise, showed reductions in resting systolic and diastolic blood pressure at rest of 11 and 8 mm Hg, respectively (184). The decrement in blood pressure evoked by exercise was in many studies not sufficient to produce normotension. Failure to show any major reductions in blood pressure following exercise training in some studies suggests that there may be subgroups of patients with hypertension, who are more responsive to the blood pressure lowering effects of exercise than others (185; 186).

To conclude, a quite strenuous exercise program is necessary in order to obtain maximal benefit of this type of intervention. Since many type 2 diabetic patients suffer from heart disease, neuropathy, and osteoarthrosis only a minority of patients with type 2 diabetes can be expected to profit from regular physical exercise. However, much more should be done to motivate younger and healthier diabetic patients for daily exercise.

7.2 OVERWEIGHT

Since overweight and obesity are strong predictors for the development of type 2 diabetes it seems obvious that treatment of overweight will have beneficial effects in type 2 diabetic patients. Weight loss has in epidemiological studies been associated with a reduction in insulin resistance and an improvement in risk factors for macro- and microvascular disease in type 2 diabetes (187). The size of the weight reduction in order to achieve clinically relevant changes in risk factors is, however, quite large around 15% of body weight. Furthermore, in intervention studies with behavioural weight-control programs it seems that type 2 diabetic patients loose less weight than their overweight non-diabetic spouses (188). Another problem in inducing weight loss in type 2 diabetic patients is the lack of studies demonstrating that the reductions in weight seen during short-term programs can be maintained in the long-term (189). A meta-analysis including 89 studies and 1800 patients with type 2 diabetes comprising studies with a duration of up to one year has investigated the effect of different treatment strategies in reducing weight in this type of patients (190). All interventions except anorectic drugs given without behaviour therapies led to reductions in mean body weight. Dietary strategies led to a mean decrease in body weight of 9 kg and were associated with the largest changes in HbA_{1c} (2.7%). Surgery had the greatest effect on weight loss with an average weight loss of 22 kg, however this result was not obtained in a randomised study. Similarly, an average weight loss of 28 kg over a ten year period with gastric surgery in overweight patients with an average BMI of 41 kg/m^2 was seen in a Swedish study with beneficial effects on hyperglycaemia and hypertension compared to a matched overweight control group receiving conventional obesity treatment with dietary advice and anorectic drugs (191; 192).

A typical finding in randomised intervention studies examining the effect of intensive blood glucose lowering with oral hypoglycaemic agents or insulin is a weight increase following treatment with

these drugs (44; 193-195). Although an increase in weight in type 2 diabetic patients is associated with deleterious effects on insulin sensitivity and aggravation of other risk factors in type 2 diabetes it should be emphasised that blood glucose lowering treatment alone (193; 195), or in combination with other treatments (44; 46) reduces the risk of long-term complications and as a consequence such a treatment should *not* be postponed or stopped because of fear of weight gain. Furthermore, we have shown that using a continuous behaviour modification strategy over an eight year period, the weight gain with intensive therapy was not significantly larger than with conventional therapy (46).

In summary, a substantial weight loss is needed to normalise risk factors in type 2 diabetes. Although induced weight changes are rarely of long lasting duration intervention may reduce the weight gain otherwise seen with intensified intervention against hyperglycaemia in type 2 diabetes. Extremely obese patients may benefit from gastric surgery.

7.3 SMOKING CESSATION

As mentioned previously several studies have demonstrated a close association between smoking and risk for CVD in both the diabetic and the non-diabetic population (196). In that respect, it is disappointing that at this time there are no randomised, controlled intervention studies that have documented the beneficial effect of giving up smoking for patients with type 2 diabetes. The most comprehensive and successful intervention study performed to date, which included both non-diabetic and diabetic patients, was the MRFIT in which 12,866 men with a high risk of developing CVD were randomised to specific intervention against multiple risk factors (smoking, hypertension, hypercholesterolemia) at a medical centre or follow-up by the general practitioner (GP) with standard intervention according to generally accepted guidelines (197). After an average follow-up period of 7 years, 50% of the men in the intervention group had stopped smoking, while the equivalent percentage in the control group was 29. Already after one year, the two groups showed significant differences in the number of smokers in the groups. Despite this large difference in the number of smokers, no significant difference in the number of deaths caused by either CVD or cancer was found. No analyses of subgroups for diabetic patients have been published. There are no obvious explanations for this disappointing result. However, one explanation could be that the study did not have sufficient power to detect a difference in the follow-up time given. Another and quite interesting aspect is that the effect of smoking cessation on CVD may be lesser the longer the duration of smoking prior to cessation. This has in epidemiological studies been demonstrated to be the case in a mixed diabetes population and most recently in women with type 2 diabetes from the Nurses' Health Study cohort (198; 199). In the mixed diabetes population study 4,427 patients were followed. All-cause mortality risks were significantly higher for recent quitters (within 1 to 9 years) with a relative risk of 1.53 compared with patients who had never smoked. In comparison, those who had quit earlier (≥10 years) had a relative risk of 1.25 compared to patients who had never smoked. Also, the mortality rate was highest in those who had smoked the longest. In the latter study 7,401 women with type 2 diabetes were followed for 20 years (199). A clear dose dependent relationship between smoking and mortality risk was seen. The overall relative risk compared to never smokers was 1.31 for past smokers compared to never smokers, 1.43 for current smokers of 1-14 cigarettes per day, 1.64 for current smokers of 15-34 cigarettes per day, and 2.19 for current smokers of more than 34 cigarettes per day. Also in this study it was found, that patients who had stopped smoking more than ten years ago still had a significantly higher risk for mortality (relative risk 1.11) than patients who had never smoked. These two studies clearly indicate, that individuals with diabetes who smoke should be encouraged to quit as soon as possible in the course of the disease.

The majority of scientific papers about diabetes and smoking has focused on reviews of the current literature and have extrapolated from other studies to include issues of particular pertinence to diabetes (196). No randomised intervention studies in type 2 diabetes have addressed the efficacy of various smoking cessation strategies. In type 1 diabetes two randomised studies found equal effect of simple advice given by a physician as compared to more sophisticated behaviour intervention strategies not using nicotine replacement therapy (200; 201). In a meta-analysis of 53 randomised trials using nicotine replacement therapy with a follow-up of at least six months this approach doubled the chance of smoking cessation, but none of the studies included reported effects from type 2 diabetic patients (202).

In the Steno-2 study we used a combination of behaviour modification strategies as well as nicotine replacement therapy in our smoking cessation programs for patients randomised to intensive multifactorial intervention. When evaluated two years after the last of two smoking cessation courses held during the trial, the smoking cessation rate in patients participating in these courses was 43% (45). In comparison, this rate has been found to be approximately 18% one year after smoking cessation in several other studies (203). However, the number of smokers was not significantly reduced in the intensive as compared to the conventional group at four or eight years after study start (44; 46).

In conclusion, although the definite proof for and size of the beneficial effects from smoking cessation need to be investigated in randomised trials, overwhelming epidemiological evidence suggests that all patients with type 2 diabetes should refrain from smoking. Since the deleterious effects of smoking persists more than ten years after quitting smoking, smoking cessation should be encouraged early in the course of the disease. However, even in patients who smoke, late diabetic complications can be reduced with intensified multifactorial intervention (46).

7.4 PHARMACOLOGICAL INTERVENTIONS

An extensive review of the many single risk factor intervention studies with special emphasis on patients with type 2 diabetes has recently been published (204). Tables 2-6 summarise the major randomised intervention studies with single risk factor treatment of hyperglycaemia, hypertension, dyslipidaemia and microalbuminuria. Preventive treatment with low-dose acetylsalicylic acid, ACE inhibitors, and treatment with vitamin C and E will be discussed below as well as certain features from single risk factor intervention trials with special relation to the interventions given in the Steno-2 study.

7.4.1 Pharmacological treatment of hyperglycaemia

Single risk factor trials intervening against hyperglycaemia are shown in Table 2. Although hyperglycaemia is a strong risk factor for micro- and macroangiopathy in type 2 diabetes, intervention against hyperglycaemia in randomised trials has only demonstrated clear effects of intervention on microangiopathy (Table 2). It is, however, of importance to notice that the blood glucose levels obtained were higher than targets according to national guidelines. However, metformin seems to pose special benefits in overweight or obese diabetic patients, yet a possible deleterious effect of this drug in patients with secondary failure to sulphonylureas needs to be elucidated.

7.4.2 Pharmacological treatment of hypertension

Besides the obvious question whether treatment of elevated blood pressure in type 2 diabetic patients reduces the risk of complications, two questions with clinical relevance concerning antihypertensive treatment of patients with type 2 diabetes should be addressed: 1) what is the desired blood pressure? (53; 205-207) and 2) which antihypertensive drug should be prescribed? (54; 208-214). Table 3 summarises some of these studies, clearly demonstrating the benefits of lowering blood pressure in patients with type 2 diabetes.

Table 2. Absolute risk, absolute risk reduction, relative risk reduction and p-values for selected endpoints in studies intervening against hyperglycaemia. Table is based on references (193; 195; 295).

	Number of patients	Follow-up time	Endpoint	Absolute risk control (%)	Absolute risk active (%)	Absolute risk reduction (%)	Relative risk reduction[a] (%)	p-value
UKPDS								
Insulin or sulfonylureas	3867	10.0 yr	Any diabetes-related endpoints[b]	38.5	35.3	3.2	12	0.03
			Diabetes-related death[c]	11.3	10.4	0.9	10	0.34
			Myocardial infarction	16.3	14.2	2.1	16	0.05
			Microvascular complications	10.6	8.2	2.4	25	0.01
Metformin (overweight)	753	10.7 yr	Any diabetes-related endpoints[b]	38.9	28.7	10.2	32	0.002
			Diabetes-related death[c]	13.4	8.2	5.2	42	0.02
			Myocardial infarction	17.8	11.4	6.4	39	0.01
			Microvascular complications	9.2	7.0	2.2	29	0.19
Kumamoto study	110	6.0 yr	Progression in urinary albumin excretion rate	30.0	9.6	20.4	68	0.005
			Progression in retinopathy	38.0	13.4	24.6	65	0.007

a) In case of discrepancy between the calculated relative risk reduction from values given in the table and the value given in the specific study the latter has been used since this value could have been adjusted for covariates.
b) Sudden death, death from hyperglycaemia or hypoglycaemia, fatal or non-fatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation (at least one digit), vitreous haemorrhage, retinal photocoagulation, blindness in one eye, or cataract extraction.
c) Death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyperglycaemia or hypoglycaemia, and sudden death.

Table 3. Absolute risk, absolute risk reduction, relative risk reduction and p-values for selected endpoints in studies randomising patients to different blood pressure levels or to active or placebo treatment with reference to evaluation of the effect of intensified blood pressure control. Table is based on references (53; 205-207).

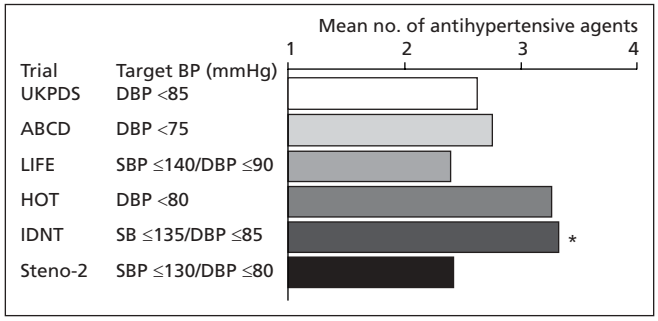
	Number of patients	Follow-up time	Endpoint	Absolute risk control (%)	Absolute risk active (%)	Absolute risk reduction (%)	Relative risk reduction[a] (%)	p-value
UKPDS[b]	1148	8.4 yr	Any diabetes-related endpoints[c]	43.5	34.2	9.3	24	0.005
			Diabetes-related death[d]	15.9	10.8	5.1	32	0.02
			Myocardial infarction	17.7	14.1	3.6	31	0.13
			Microvascular complications	13.8	9.0	4.8	37	0.01
HOT								
All patients	18790	3.8 yr	Major cardiovascular event	3.7	3.6	0.2	5	0.50
Diabetic patients	1501	3.7 yr	Major cardiovascular event	9.0	4.4	4.6	51	0.005
SHEP								
Non-diabetic patients	4736	4.5 yr	All cause mortality	10.2	9.0	1.2	15	NS
			Cardiovascular event	17.4	12.2	5.2	24	<0.05
Diabetic patients	583	4.7 yr	All cause mortality	16.0	13.8	2.2	24	NS
			Cardiovascular event	27.7	20.1	7.6	34	<0.05
Syst-Eur								
All patients	4695	2.0 yr	All cause mortality	6.0	5.1	0.9	15	0.50
			Cardiovascular mortality	3.4	2.5	0.9	26	0.32
Diabetic patients	492	2.0 yr	All cause mortality	10.8	6.3	4.5	41	0.09
			Cardiovascular mortality	6.7	2.0	4.7	55	0.01

a) In case of discrepancy between the calculated relative risk reduction from values given in the table and the value given in the specific study the latter has been used since this value could have been adjusted for covariates.
b) Only patients with diabetes have been included in the study.
c) Sudden death, death from hyperglycaemia or hypoglycaemia, fatal or non-fatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation (at least one digit), vitreous haemorrhage, retinal photocoagulation, blindness in one eye, or cataract extraction.
d) Death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyperglycaemia or hypoglycaemia, and sudden death.

7.4.2.1 Dual blockade with ACE inhibitors and angiotensin II receptor blockers in type 2 diabetes

The theoretical background for the use of dual blockade of the renin-angiotensin system is the existence of non-ACE pathways in the formation of angiotensin II. By combining two different pharmacological principles and inhibiting both the ACE and the angiotensin II type 1 receptor, it seems possible to arrive at a treatment regimen that inhibits both the production and the action of angiotensin II. The efficacy of this approach has been investigated in two larger trials in type 2 diabetes. Although promising results with dual blockade with respect to lowering of blood pressure compared to either agent alone (candesartan or lisinopril) was seen in a short-term trial of 12 weeks in 197 hypertensive type 2 diabetic patients with microalbuminuria in the Candesartan and Lisinopril Microalbuminuria study (CALM) (91) this result could not be confirmed in another trial by the same group with 12 months of follow up in a mixed population of 75 patients with diabetes (215). However, a smaller study in type 2 diabetic patients with nephropathy has suggested that UAER is reduced significantly more with an angiotensin II receptor blocker added to maximal doses of an ACE inhibitor despite no significant reductions in blood pressure (216).

To conclude, from post-hoc subgroup analyses of intervention studies and the UKPDS there is evidence that intensive blood pressure lowering treatment reduces the risk of micro- as well as macrovascular complications. The risk for neither type of complication proved to have a lower threshold value for blood pressure, indicating that target for the treatment may be set at a low level. There seems to be no special advantages or disadvantages derived from the antihypertensive drugs used, although treatment with short-acting calcium antagonists should be avoided. The decisive factor for measuring the effect seems to be the level of blood pressure obtained rather than the specific antihypertensive drug used. As pointed out in Figure 1 the majority of hypertensive type 2 diabetic patients will require more than one antihypertensive drug to obtain satisfactory blood pressure control. Future studies should therefore be designed to examine whether special combinations of antihypertensive drugs present any special advantages or disadvantages.



*) In addition to study drug
DBP: diastolic blood pressure
SBP: systolic blood pressure
UKPDS: United Kingdom Prospective Diabetes Study (207)
ABCD: Appropriate Blood Pressure Control in Diabetes (209)
LIFE: Losartan Intervention For Endpoint reduction in hypertension study (211)
HOT: Hypertension Optimal Treatment study (245)
IDNT: Irbesartan Diabetic Nephropathy Trial (241)

Figure 1. The number of blood pressure lowering agents used in the active treatment arm in order to achieve blood pressure goals in selected randomised trials enrolling a large proportion of patients with type 2 diabetes. Based on references (46; 207; 209; 211; 241; 245).

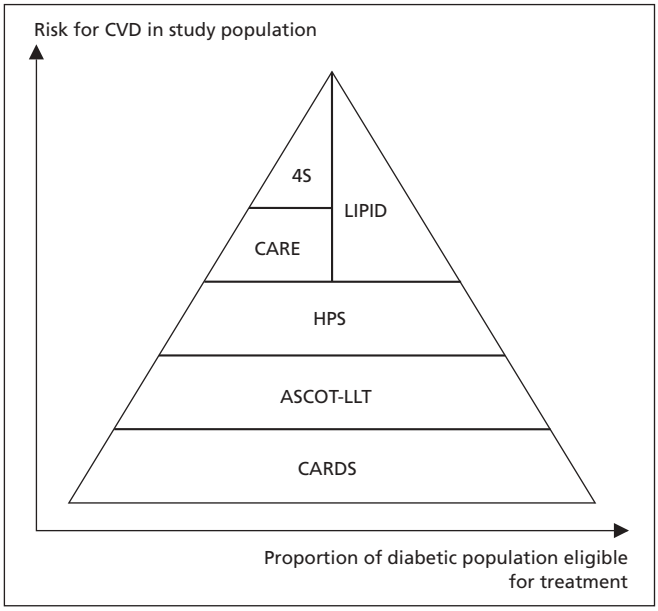
7.4.3 Pharmacological treatment of dyslipidaemia

The use of pharmacological intervention with statins in the prevention of CVD has been extensively examined, especially in patients with previous known ischaemic heart disease (secondary prevention) (217-226). However, only one study has investigated the effect of *primary* pharmacological intervention with statins solely in patients with type 2 diabetes (227), and only a few have investigated the effects of fibrates as secondary intervention (228-230), and as a consequence current recommendations are based on subanalyses from larger studies including patients with diabetes. Results from these studies are summarised in Table 4.

The above mentioned trials have with the exception of one (224) prescribed a fixed statin dose, thus leaving open the question of the optimal dose for the different statins. Furthermore, studies comparing different statins in equipotent doses are also missing. One study has compared the effect of intensive versus moderate lipid lowering treatment after acute myocardial infarction using two different statins in non-equipotent doses. The Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction 22 (PROVE IT – TIMI 22) trial compared the effect of 40 mg of pravastatin daily with 80 mg of atorvastatin daily in 4,162 patients with an acute coronary syndrome (231). The primary endpoint consisted of all cause mortality, myocardial infarction, documented unstable angina requiring rehospitalisation, revascularisation, and stroke. Eighteen percent of patients included had diabetes at randomisation. During a follow-up of two years 26.3% of patients in the standard dose pravastatin group had an event compared to 22.4% in the high-dose atorvastatin group, representing a 16% relative risk reduction in the hazard ratio favouring atorvastatin, p=0.005. The difference was seen already after 30 days of intervention. Although the risk reduction with high-dose atorvastatin was consistent among several previous specified subgroups, it was not significant in patients with diabetes (HR 0.81 (95% confidence interval 0.62-1.03)). The difference in fasting serum LDL-cholesterol was about 1 mmol/l throughout the study period.

To conclude, post hoc subgroup analyses of patients with type 2 diabetes mellitus and known ischaemic heart disease with normal or raised fasting serum total cholesterol values or too low fasting serum HDL-cholesterol values have documented the beneficial effect of *secondary* prevention using statins or fibrates. The effect of fibrates as *primary* prevention of ischaemic vascular disease has not been documented. A significant effect of simvastatin as primary prevention in the subgroup of patients with diabetes and a non-fasting serum cholesterol level above 3.5 mmol/l has been shown in the Heart Protection Study (232), while the Collaborative Atorvastatin Diabetes Study found a significant effect of primary prevention with atorvastatin in type 2 diabetic patients with modest elevations of fasting serum LDL-cholesterol (227). As a consequence these findings have triggered the discussion whether all patients with diabetes should be given statin treatment as *primary* prevention. If it can be replicated, that the absolute risk reductions for coronary heart disease with statin treatment is the same throughout the spectre of fasting serum cholesterol concentrations as suggested in the Heart Protection Study (HPS) (232) as well as in the Collaborative Atorvastatin Diabetes Study (CARDS) (227), it indeed seems favourable to give all patients with type 2 diabetes a statin as *primary* prevention. However, it should be mentioned that the subgroup analyses in patients with diabetes in both the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) (225) and the The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT) (226) did not show significant risk reductions with statin treatment as primary prevention. However, the current evidence based on less rigorous inclusion criteria in the studies suggests that patients with type 2 diabetes should be treated with a statin as primary prevention unless their risk for cardiovascular disease is found sufficiently low to withhold such a treatment (Figure 2).

Fasting serum LDL-cholesterol levels serve in most guidelines as an indicator for cholesterol-lowering therapy, since a linear relationship between reduction in fasting serum LDL-cholesterol level and the size of risk reduction in CVD has been demonstrated (233). However, large clinical trials indicates that statin-treated individuals have significantly less CVD than patients with comparable serum cholesterol levels (221). Experimental data have shown that statins exhibit pleiotropic effects that can beneficially impact occlusive vascular disease, including inhibition of smooth muscle proliferation



4S: *Scandinavian Simvastatin Survival Study.* Secondary intervention. Total-cholesterol between 5.5 and 8.0 mmol/l.
CARE: *Cholesterol And Recurrent Event Trial.* Secondary intervention. Total-cholesterol less than 6.2 mmol/l.
LIPID: *Long-Term Intervention with Pravastatin in Ischaemic Disease.* Secondary intervention. Total-cholesterol between 4.0 and 7.9 mmol/l.
HPS: *Heart Protection Study.* Mixed primary and secondary intervention. Total-cholesterol above 3.5 mmol/l.
ASCOT-LLT: *Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Trial.* Primary intervention, but with hypertension. Total-cholesterol less than 6.5 mmol/l.
CARDS: *Collaborative Atorvastatin Diabetes Study.* Primary intervention. LDL-kolesterol less than 4.1 mmol/l.

Figure 2. The historical aspect in lipid-lowering trials in type 2 diabetic patients is shown in the figure with the initial trials in the top of the pyramid including high-risk patients while later trials have included patients at much lower risk thereby broadened the population eligible for drug treatment with statins. Figure is based on references (220-223; 225; 227).

Table 4. Absolute risk, absolute risk reduction, relative risk reduction and p-values for selected endpoints from the in the review described studies intervening against dyslipidaemia. Table is based on references (217-223; 225-229).

	Number of patients	Follow-up time	Endpoint	Absolute risk control (%)	Absolute risk active (%)	Absolute risk reduction (%)	Relative risk reduction[a] (%)	p-value
Primary prevention – Fibrate								
Helsinki Heart Study								
All patients	4081	5.0 yr	Myocardial infarction or cardiovascular death	4.1	2.7	1.4	34	<0.02
Diabetes patients	135	5.0 yr	Myocardial infarction or cardiovascular death	10.5	3.4	7.1	68	0.19
SENDCAP[b]	164	3.0 yr	Incidence of myocardial infarction or ischaemia in ECG	19.3	6.2	13.1	68	0.01
Primary prevention – Statins								
AFCAPS/TexCAPS								
All patients	6605	5.2 yr	First major cardiovascular event	5.5	3.5	2.0	37	<0.001
Diabetes patients	155	–	First major cardiovascular event	8.5	4.8	3.7	44	NS
CARDS[b]	2838	3.9 yr	Major coronary event	9.0	5.8	3.2	37	0.001
Secondary prevention – Fibrate								
VAHIT								
All patients	2531	5.1 yr	Myocardial infarction. stroke or cardiovascular death	26.0	20.4	5.6	22	<0.001
Diabetes patients	627	–	Myocardial infarction. stroke or cardiovascular death	36.5	28.5	8.0	22	0.05
Secondary prevention – Statins								
4 S								
All patients	4444	5.4 yr	Major cardiovascular event	22.6	15.9	6.7	30	<0.0001
Diabetes patients	202	5.4 yr	Major cardiovascular event	45.4	22.9	22.5	55	0.002
CARE								
All patients	4159	5.0 yr	Myocardial infarction or cardiovascular death	13.2	10.2	3.0	23	0.003
Diabetes patients	586	–	Myocardial infarction or cardiovascular death	36.8	28.7	8.1	22	0.05
LIPID								
All patients	9014	6.1 yr	Myocardial infarction or cardiovascular death	8.3	6.4	1.9	24	<0.001
Diabetes patients	782	–	Myocardial infarction or cardiovascular death	22.8	19.2	3.6	19	NS
Heart Protection Study								
All patients	20536	5 yr	First major vascular event	25.2	19.8	5.4	21	<0.001
Diabetes without CVD	3982	5 yr	First major vascular event	18.6	13.8	4.8	26	<0.05
Diabetes with CVD	1981	5 yr	First major vascular event	37.8	33.4	4.4	12	<0.05
ALLHAT								
All patients	10355	4.8 yr	Total mortality	15.3	14.9	0.4	1	0.88
All patients	10355	4.8 yr	Major cardiovascular event	10.4	9.3	1.1	9	0.16
ASCOT-LLA								
All patients	19342	3.3 yr	Fatal CHD and non-fatal myocardial infarction	3.0	1.9	2.1	36	0.0005
Diabetes patients	2532	3.3 yr	Fatal CHD and non-fatal myocardial infarction	3.6	3.0	0.6	16	0.43

a) In case of discrepancy between the calculated relative risk reduction from values given in the table and the value given in the specific study the latter has been used since this value could have been adjusted for covariates.
b) Only patients with diabetes have been included in the study.
– Indicates that follow-up time for the diabetic subpopulation has not been given or cannot be estimated from information available.

and platelet aggregation, enhancement of endothelial function, and antiinflammatory actions (234-236). Thus, there appears to be a growing list of actions that are attributed to statins beyond their ability to reduce serum cholesterol levels. It remains to be determined, however, which, if any, of these effects are actually clinically important at the dose range used.

In the discussion whether treatment should be simvastatin or another statin it should be recalled, that the effect of simvastatin has been proven in a single risk factor intervention trial. The typical type 2 diabetic patient will take several drugs to diminish the impact of several risk factors. In the Steno-2 study where multiple risk factor intervention in type 2 diabetic patients with and without known CVD at baseline was associated with an absolute risk reduction of 20% for CVD during eight years, the statin used was atorvastatin (46).

7.4.4 Specific treatment of elevated urinary albumin excretion rate in type 2 diabetes

Specific treatment of microalbuminuria (UAER between 30 and 300 mg per 24 hour) with ACE inhibitors in intervention studies of patients with type 1 diabetes have proven to possess a albuminuria reducing effect in normotensive as well as hypertensive patients, an effect found to be independent of the antihypertensive effect of the ACE inhibitors (237; 238).

Even though a significant risk reduction in developing dialysis-dependent kidney disease or cardiovascular morbidity and mortality following treatment with ACE inhibitors has not yet been established, ACE inhibitors are now widely used as standard intervention in patients with type 1 as well as type 2 diabetes complicated by microalbuminuria, regardless of the presence of hypertension. Studies that form the evidence for the treatment effect of blocking the

Table 5. Absolute risk, absolute risk reduction, relative risk reduction and p-values for selected endpoints in studies with specific intervention against increased urinary albumin excretion rate in type 2 diabetic patients. Table is based on references (92; 296-298).

	Number of patients	Follow-up time	Endpoint	Absolute risk control (%)	Absolute risk active (%)	Absolute risk reduction (%)	Relative risk reduction[a] (%)	p-value
Ravid-study								
Enalapril vs. placebo	94	6 yr	Progression to nephropathy	19.0	6.5	12.5	66	0.04
IRMA-2								
Irbesartan 150 mg vs. placebo	396	2 yr	Progression to nephropathy	14.9	9.7	5.2	39	0.08
Irbesartan 300 mg vs placebo	395	2 yr	Progression to nephropathy	14.9	5.2	9.7	70	<0.001
RENAAL								
Losartan vs. placebo	1513	3.4 yr	Major renal event or death	47.1	43.5	3.6	16	0.02
IDNT								
Irbesartan vs. placebo	1148	2.6 yr	Major renal event or death	39.0	32.6	6.4	20	0.02
Irbesartan vs. amlodipine	1146	2.6 yr	Major renal event or death	41.1	32.6	8.5	23	0.006

a) In case of discrepancy between the calculated relative risk reduction from values given in the table and the value given in the specific study the latter has been used since this value could have been adjusted for covariates.

Table 6. Absolute risk, absolute risk reduction, relative risk reduction and p-values for selected endpoints in studies comparing acetylsalicylic acid and placebo. Table is based on references (243-247).

	Number of patients	Follow-up time	Endpoint	Absolute risk control (%)	Absolute risk active (%)	Absolute risk reduction (%)	Relative risk reduction[a] (%)	p-value
HOT								
All patients	18790	3.8 yr	Major cardiovascular events	3.9	3.4	0.5	15	0.03
		3.8 yr	Myocardial infarction	1.4	0.9	0.5	36	0.002
Primary Prevention Project								
All patients	4495	3.6 yr	Major cardiovascular events	8.2	6.3	1.9	23	<0.05
US Physicians' Health Study								
All patients	22071	5.2 yr	Myocardial infarction	2.3	1.3	1.0	44	<0.001
Diabetes patients	533	–	Myocardial infarction	10.1	4.0	6.1	61	0.22
Women's Health Study								
Non-diabetic subjects	38825	10.1 yr	Major cardiovascular events	2.4	2.2	0.2	10	0.13
Diabetes patients	1027	10.1 yr	Major cardiovascular events	12.1	11.3	0.8	10	0.57
Non-diabetic subjects	38825	10.1 yr	Stroke	1.2	1.1	0.1	13	0.15
Diabetes patients	1027	10.1 yr	Stroke	6.0	2.9	3.1	54	0.01
ETDRS								
All patients	3711	5 yr	Myocardial infarction	12.3	9.1	3.2	17	<0.05
Type 2 diabetes	1152	5 yr	Myocardial infarction	8.1	6.0	2.1	17	NS

a) In case of discrepancy between the calculated relative risk reduction from values given in the table and the value given in the specific study the latter has been used since this value could have been adjusted for covariates.
– Indicates that follow-up time for the diabetic subpopulation has not been given or cannot be estimated from information available.

renin-angiotensin system are summarised in Table 5 (92; 211; 239-241).

To conclude, there is strong evidence that the angiotensin II receptor antagonists pose albuminuria reducing effects beyond that of blood pressure lowering alone in type 2 diabetes. Whether a similar effect of ACE inhibitors exists is not known. No studies have compared ACE inhibitors and angiotensin II receptor antagonist head-to-head in a randomised trial in type 2 diabetes. In our Steno-2 study all patients in the intensive therapy group were prescribed an ACE inhibitor (captopril) because of the presence of microalbuminuria. Significant reductions in the risk for nephropathy were seen both after four and eight years of intervention, respectively, with intensive compared to conventional treatment. However, while none of the patients received combined treatment with an ACE inhibitor and an angiotensin II receptor antagonist after four years, this was the case for 28% of the patients in the intensive arm and for none of the patients in the conventional treatment arm at the end of the trial.

7.4.5 Preventive treatment using low-dose acetylsalicylic acid

The value of ASA as *secondary* cardiovascular prevention in diabetes is indisputable (242). As seen from Table 6 *primary* prevention treatment with low-dose ASA in diabetic patients showed an effect in three of the reported studies described (243-247). By inhibiting platelet activation treatment with low-dose ASA is associated with a significantly increased risk of gastrointestinal bleedings requiring transfusions as well as epistaxis, haematuria, and easy bruising. Absolute risk reductions are larger in high risk patients, thereby diminishing the role of side-effects. As a consequence, low-dose ASA should only be considered as primary prevention to patients with type 2 diabetes having a Framingham point score (appendix 2) above 0.6% per year (248).

7.4.5.1 Does treatment with low-dose acetylsalicylic acid interfere with diagnosis and monitoring of micro- or macroalbuminuria in type 2 diabetes?

High dose treatment with ASA and other inhibitors of the enzyme cyclooxygenase have been shown to reduce UAER in type 1 diabetic patients. We investigated whether this also applied for low-dose treatment with ASA in type 2 diabetic patients with elevated levels of UAER (51). In a cross-over study 31 patients with micro- or macroalbuminuria but without ACE inhibitor treatment were randomised to four weeks of treatment with aspirin 150 mg daily followed by four weeks of placebo after a 2 week wash-out period, or vice versa. During treatment with aspirin a non-significant reduction of 2% compared to placebo was seen in UAER. Similarly, no changes in glomerular filtration rate or serum creatinine were observed during aspirin treatment. We therefore concluded that low-dose treatment with ASA does not interfere with the diagnosis and

monitoring of UAER in type 2 diabetic patients. Because of our study design, we could not investigate the effect of aspirin given on top of treatment with ACE inhibitors.

7.4.6 Preventive treatment with ACE inhibitors

The Heart Outcomes Prevention Evaluation (HOPE) Study was based on the hypothesis that the renin-angiotensin-aldosterone system plays a vital role in the development of CVD (249). A total of 9,297 patients were randomised to double-blind treatment with ramipril or placebo. All patients included suffered from known CVD or diabetes with at least one additional risk factor (hypertension, increased fasting serum total-cholesterol, low fasting serum HDL-cholesterol, microalbuminuria or smoking) and were therefore at high risk of cardiovascular events. The primary endpoint consisted of a combination of myocardial infarction, stroke or death caused by cardiovascular disease. Also a 26% relative risk reduction (p=0.03) was found in the number of patients with diabetes-related complications, defined as 24-hour UAER >300 mg or 24-hour urinary protein excretion >500 mg, dialysis-dependent kidney insufficiency and photocoagulation caused by retinopathy. No results are available for this endpoint in terms of diabetic patients without diagnosed heart disease. A subgroup analysis in a separate paper reported a significant 25% relative risk reduction for the primary CVD endpoint with ramipril treatment compared with placebo in patients with diabetes (250). Since blood pressure did not differ significantly between treatment groups this difference cannot directly be explained by a difference of standard blood pressure measures in the main study. However, a subgroup analysis in 38 patients showed a significantly lower 24 hour blood pressure profile (10/4 mm Hg, p=0.03) in patients treated with ramipril compared to placebo (251). Similarly, when focusing only on diabetic patients without previously known cardiovascular disease but with at least one of the earlier mentioned risk factors, no significant difference between ramipril treatment and placebo was found.

An eightfold lower dose of ramipril was used in the the Non-insulin-dependent diabetes, hypertension, microalbuminuria or proteinuria, cardiovascular events, and ramipril (DIABHYCAR) study enrolling almost 5,000 patients with type 2 diabetes and persistent microalbuminuria or proteinuria (252). The primary endpoint was the combined incidence of cardiovascular death, non-fatal myocardial infarction, stroke, heart failure leading to hospital admission, and ESRD. Despite small reductions in both systolic and diastolic blood pressure during a median follow-up time of four years, no risk reductions were seen for the combined endpoint or the components of the endpoint. However, low-dose ramipril favoured regression from microalbuminuria and proteinuria to lower levels of UAER.

To conclude, based on the HOPE study it is recommended that diabetic patients should be offered treatment with ACE inhibitors as secondary prevention of CVD, while there is no evidence to support the use of ACE inhibitors as primary prevention of CVD.

7.4.7 Treatment with antioxidant vitamins E and C

7.4.7.1 Effect on cardiovascular disease

The enthusiasm for high-dose vitamin E in the secondary prevention of CVD was fuelled by a publication of the Cambridge Heart Antioxidant Study (CHAOS) (253) reporting a 50% relative risk reduction in myocardial infarction during 1,4 years of supplementation with vitamin E 800 IE/day compared to placebo; later confirmed with an almost similar result in the SPACE (secondary prevention of cardiovascular disease in endstage renal disease) study (254). However, during recent years several negative trials in term of cardiovascular outcomes have washed the flames away. Thus results from large scale studies such as the HOPE Study (255), the HPS (232), the GISSI-prevenzione trial (256), and the Primary Prevention Project (246) all investigating the effect of different doses of vitamin E on cardiovascular outcomes have all shown a lach of effect. An important aspect in the HPS, where active treatment was a daily supplementation of 600 mg vitamin E, 250 mg vitamin C, and 20 mg beta-carotene was the effect of the antioxidant supplementation on the lipid profile. The small but significant increases in plasma LDL-cholesterol and triglycerides seen in combination with a significant fall in plasma HDL-cholesterol during antioxidant treatment call for caution, since prolonged routine treatment with these vitamins may lead to an increase in vascular disease.

7.4.7.2 Effect on kidney function

Intake of 500 mg of vitamin C twice daily has been reported to decrease UAER in a small but randomised study in 20 diabetic patients (18 patients had type 2 diabetes) with microalbuminuria or retinopathy (257). The reduction was seen after 9 months of treatment and throughout the rest of the 12 months study period.

A subgroup analysis of 3,654 primarily type 2 diabetic patients participating in the HOPE study demonstrated no effect for a combined endpoint of diabetic microvascular complications (overt nephropathy, dialysis, and laser therapy) in patients receiving 400 units of vitamin E daily for 4.5 years (255). However, the exact number of patients with the different complications is not given in the paper. No information on compliance and plasma values of vitamin E has been reported.

Despite the negative result of the HOPE study, it is, however, still possible that vitamin E supplementation requires co-supplementation with other antioxidants to have beneficial effects. We examined the effects of a combination of high dose vitamin C (1250 mg/day) and vitamin E (680 units/day) on kidney function in a randomised, placebo-controlled, double-blind, cross-over study (50). A total of 29 patients with type 2 diabetes were randomised to four weeks of active treatment followed by a three week wash-out period before placebo tablets, or vice versa. We found a significant reduction in UAER of 19% during short-term active treatment compared to placebo. As opposed to the previous study by McAuliffe et al the decrease in UAER in our study did not correlate to the rise in, or the obtained fasting plasma concentrations of vitamin C. The effect of vitamin supplementation on UAER was also seen within the first four weeks of treatment in our short-term study. No changes were seen for serum creatinine.

To conclude, ingestion of antioxidants does not seem to reduce the risk for CVD in type 2 diabetes, although an effect in highly selected patient groups cannot be excluded. The potential impact of antioxidants on kidney function in type 2 diabetic patients with or without elevated levels of UAER needs further investigation.

8. INTENSIFIED MULTIFACTORIAL INTERVENTION IN TYPE 2 DIABETES

Based on the results from single risk factor intervention trials national guidelines recommend intensified multifactorial intervention of several concomitant risk factors for late diabetic complications in type 2 diabetes, although the outcome of this approach has only been investigated in a few studies in type 2 diabetes. In this respect several questions arise: a) what are the benefits of intensified multiple risk factor intervention on morbidity and mortality?, b) who will benefit the most of such an intervention?, c) will a formalised intervention program work in general practice?, d) are there any problems with the adherence to lifestyle and multiple drug treatment?, e) are there any side effects?, f) do drug interactions pose a risk?, and g) what are the costs of such an intervention at the community or patient level?

Six studies have investigated the effect of intervention comprising both behaviour modification and polypharmacy specifically in patients with type 2 diabetes with follow-up periods ranging from one to 7.8 years with two of the studies including patients with newly diagnosed type 2 diabetes (25; 170) (46; 258-260).

The Diabetes Intervention Study was a randomised five-year trial with the primary aim of testing the effect of intensified health edu-

cation in improving metabolic regulation and reducing the level of coronary risk factors and incidence of ischaemic heart disease (170). A total of 1139 patients aged 30 to 55 years with newly diagnosed type 2 diabetes were randomised to a control group (n=378) receiving standard treatment at different diabetes outpatient clinics in Germany or an intervention group (n=761) receiving structured intensified health education including dietary advice, antismoking and antialcohol education and ways to increase physical activity. Guidelines for drug treatment of hyperglycaemia and hypertension were in principle the same for both groups, but within the intervention group patients were also randomised to treatment with clofibric acid 1.6 g daily or placebo. Patients in the intervention group were seen every third month. At the end of follow-up the only significant difference in diet was in the ratio polyunsaturated to saturated fat which increased significantly more in the intervention group. No difference was seen for daily intake of energy, cholesterol, or alcohol. Also physical activity increased significantly more with intensive education, whereas the amount of tobacco use only decreased significantly more than the control group in the patients in the intensive group who were randomised to treatment with clofibric acid. Fasting serum cholesterol levels increased significantly in both the control and the intervention group, which was also the case for fasting serum levels of triglycerides. However, the increase in fasting serum triglycerides was lower in the intensive group, but not lower with clofibric acid compared to placebo. Both systolic and diastolic blood pressure decreased significantly more with intensive therapy compared to placebo. Similarly, although an increase in fasting blood glucose was seen over the study period in both groups, this increase was significantly lower in the intervention group with fewer patients receiving glucose lowering drugs. The incidence of cardiovascular disease during the study period was not lower in the intervention group.

Multiple risk factor intervention was also undertaken in the study Diabetes Care in General Practice, which was a randomised controlled trial of structured personal care in type 2 diabetes mellitus enrolling 1,263 patients with newly diagnosed type 2 diabetes (25). In the routine care group doctors were free to chose any treatment and change it over time according to national guidelines. After the end of the recruitment phase the control group did not have any contact with the steering committee until the final examinations. In the structured care group patients were seen every third month and once a year patients were screened for diabetic complications. At the end of follow-up after six years the only significant differences between groups were seen for fasting plasma glucose, HbA_{1c}, and systolic blood pressure. No differences between groups were found for diet, exercise, smoking habits, fasting serum cholesterol and triglycerides, and diastolic blood pressure. The only drug used significantly more in the structured care group was metformin. No difference between groups was seen for clinical endpoints.

Another trial in a general practice setting was carried out over one year under routine clinical practice conditions with visits every third month following clinical guidelines from Spain (258). Almost 3,500 patients with type 2 diabetes were included in this non-randomised prospective trial. At the end of follow-up significant reductions were seen in blood pressure, HbA_{1c} and fasting serum lipid levels, but not in body weight. Only 16% of men and 10% of women obtained the primary aim of a predicted 10 year cardiovascular risk of less than 10%. However, a significant decline in the number of patients reducing their 10 year risk from being above 20% to being in the interval 10-20% was seen (258).

In a recent study from Israel the primary aim was to examine whether motivating type 2 diabetic patients to gain expertise about the disease would attenuate the course of late complications during a follow-up period of 7.7 years (260). One hundred and sixty-five patients were randomised to standard consultation at a diabetes clinic or a patient participation program with two 2-hour individual education sessions focused on ways to achieve tight regulation of modifiable risk factors, but with follow-up education given by primary care physicians. Patients in both groups were seen annually at the diabetes clinic, but with patients from the program group having the possibility of contacting the consultation team at the diabetes clinic whenever necessary. During follow-up patients in the program group initiated an average of 1.2 additional visits per patient per year resulting in significantly lower values of blood pressure, fasting serum LDL-cholesterol and plasma glucose level, and a relative reduction in the risk for nephropathy of 50%, a relative reduction in the risk for retinopathy of 40% as well as a relative risk reduction of 35% for a combined cardiovascular endpoint (260).

Patients included in the Steno-2 study differed from patients in the previous studies with patients being in a later stage of the disease and with a high risk of CVD, since a major inclusion criterion was microalbuminuria (44; 46). Patients were randomised to conventional treatment at their GP following national guidelines (n=80), or intensified multifactorial intervention comprising both behaviour modification and polypharmacy of several concomitant risk factors by a specialised diabetes team with consultations every third month. The protocol specified two major analysis: 1) a microvascular analysis after four years of intervention with development of diabetic nephropathy as the primary outcome (44), development or progression in retinopathy and neuropathy as secondary endpoints, and 2) a macrovascular analysis after eight years of intervention with the incidence of a composite endpoint of cardiovascular mortality, myocardial infarction, stroke, revascularisation, and amputation as the primary endpoint (46).

A significantly larger reduction in the ratio of daily intake of saturated and unsaturated fatty acids was seen both at the four and eight year examination in the intensive therapy group. However, there were no significant differences in exercise or smoking behaviour between the two groups, despite the many resources spent on behaviour modification (45). In contrast, a marked effect was seen on other risk factors. At four years of intervention the groups differed significantly for fasting blood glucose, HbA_{1c}, systolic blood pressure, fasting values of serum total cholesterol, LDL-cholesterol, and triglycerides, and UAER. At the eight year examination this was still the case, and furthermore the difference in diastolic blood pressure between the groups was statistically significant in favour of intensive therapy. Significant effects of the intensive multifactorial intervention were also seen on the primary and secondary endpoints at both of the major endpoint examinations after four and eight years of intervention, respectively. After both four and eight years of intervention relative risk reductions around 50% were seen for the development of nephropathy as well as for development or progression in retinopathy and autonomic neuropathy (Figure 3). At the end of follow-up a significant relative risk reduction of 53% (absolute risk reduction 20%) was achieved for the composite cardiovascular endpoint with intensified multifactorial intervention (46) (Figure 4).

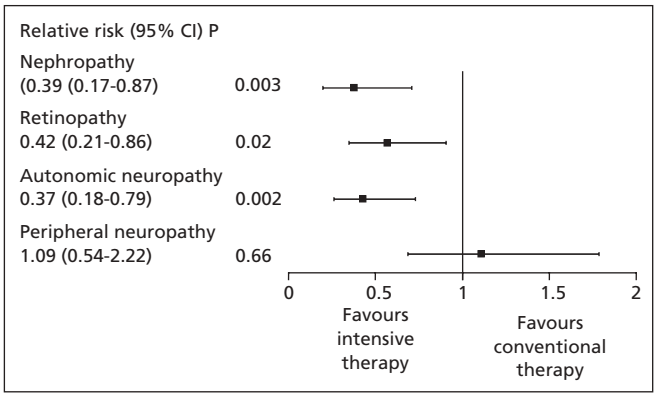


Figure 3. The relative risk of the development or progression of nephropathy, retinopathy, and autonomic and peripheral neuropathy during the average follow-up of 7.8 years in the intensive therapy group, as compared with the conventional therapy group in the Steno-2 study (46).

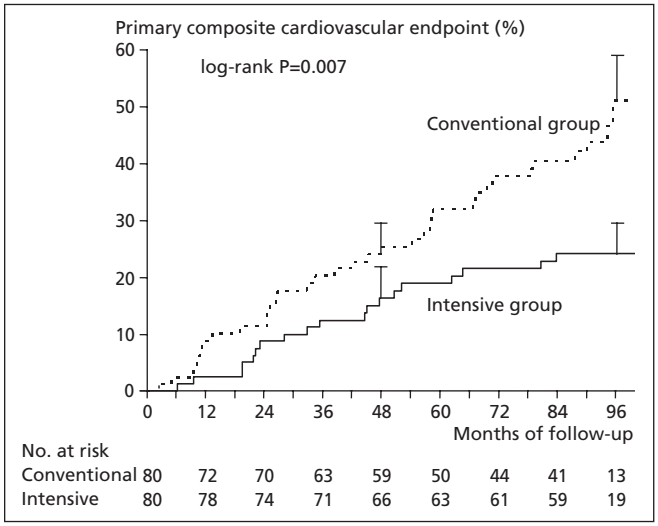


Figure 4. Kaplan–Meier estimates of the composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction, coronary-artery bypass grafting, percutaneous coronary intervention, nonfatal stroke, amputation, or surgery for peripheral atherosclerotic artery disease in the conventional therapy group and the intensive therapy group in 160 patients with type 2 diabetes and microalbuminuria in the Steno-2 study (46).

The decline in GFR did not differ between the two treatment groups in the Steno-2 study during follow-up. However, a subanalysis examining the prognostic role of remission to normoalbuminuria demonstrated, that patients who achieved remission to normoalbuminuria during multifactorial intervention had a significantly smaller annual decline in GFR compared to patients who remained microalbuminuric (47). In contrast, patients who progressed to overt macroalbuminuria had a significantly larger decline in GFR than patients remaining microalbuminuric, thus demonstrating the strength of UAER as a monitoring tool for kidney function during intervention.

While patients in the Steno-2 study all had microalbuminuria at baseline, other studies have used diabetic nephropathy as an inclusion criterion (259). In a study 90 patients were randomised to intensive treatment or to a control group and followed for two years. Treatment goals were similar within the two groups but with more frequent visits in the intensive group. The primary endpoint was the rate of progression of renal disease. The intensive therapy group had lower values of systolic and diastolic blood pressure and fasting total serum cholesterol level, but no difference was seen for glucose regulation with an HbA_{1c} level of 8.2%. At two years the estimated creatinine clearance in the intensive therapy group was 47 ml/min/month compared to 42 ml/min/month in the control group, p=0.043. New cardiovascular events (sudden death, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, coronary artery bypass grafting, amputation or interventional vascular surgery, and admission for congestive heart failure) were also fewer in the intensive group (13 compared to 21, p=0.038); yet the major difference was in the number of patients with admissions for heart failure (259).

8.1 WHICH CONCLUSIONS CAN BE DRAWN FROM MULTIFACTORIAL INTERVENTION TRIALS?

Which conclusions can be drawn from these studies in trying to answer some of the questions mentioned earlier? First, all six studies demonstrated that risk factor intervention against several concomitant risk factors can be done both at the level of general practitioners and at diabetes clinics with the Steno-2 study being the most successful in the number of risk factors reduced. Secondly, both the Steno-2 study and the study from Israel demonstrated benefits on morbidity of intensified multifactorial intervention with significant risk reductions of both cardiovascular disease as well as microvascular complications. This was, however, not the case for the two studies including patients with newly diagnosed type 2 diabetes. An obvious explanation for this discrepancy is the much higher number of risk factors reduced in the Steno-2 study, and the much larger reductions in these risk factors with intensified therapy in this study. Other studies used guidelines with risk factor targets for the intervention groups that were similar to the ones used in the control groups, thereby in itself diminishing the effect of intensified intervention. Also, a time gap from new pieces of clinical evidence are made until implementation in national guidelines will of course always exist, withholding patients in the intervention groups the benefits of new knowledge. As an example the optimal goal for fasting serum total cholesterol in the structured care group in Diabetes Care in General Practice was 6 mmol/l although several studies indicated that a much lower value should be strived for (25). Similarly, the goal for systolic and diastolic blood pressure was set high in this as well as in the Diabetes Intervention Study (170). As discussed in an earlier chapter intervention against dyslipidaemia and blood pressure has proven to have a pronounced impact as single risk factor interventions in patients with type 2 diabetes, whereas intervention against hyperglycaemia was not as effective as expected from epidemiological studies. As a consequence, one explanation for the lack of effect of intensified multifactorial intervention in patients with newly diagnosed type 2 diabetes is that these studies have not been sufficiently aggressive and proactive in their target settings.

Patients in the Steno-2 study were at higher risk for late diabetic complications than patients in the other studies, since patients in the Steno-2 study were selected because of microalbuminuria, thereby increasing the statistical power to detect differences in endpoints between the two treatment groups. Thus, with our present knowledge the questions a) and b) asked in the beginning of the chapter cannot be fully answered. Clear benefits of multifactorial intervention have been shown in a subgroup of patients with elevated UAER. These patients may comprise up to one third of patients with type 2 diabetes (16). However, further studies are needed before intensified multifactorial intervention can be recommended to patients with newly diagnosed type 2 diabetes, unless of course other important risk factors are present. It is of outmost importance, that the study design of new studies will allow sufficient separation in many risk factors between treatment groups.

The question whether an intensified risk factor intervention can be given at the level of general practitioners has also been confirmatory answered (25; 258; 260). However, a recent cross sectional study from the UK has demonstrated that it is absolutely essential to increase focus and intensify treatment of type 2 diabetes in general practice (261). A population of almost 8,000 patients with type 2 diabetes attending a total number of 42 general practices were included in the study. Thirty-one percent of all patients with type 2 diabetes were treated with diet only. More than four-fold variation between practices existed (range 15.6-73.2%). Patients treated with diet only were much less likely to have HbA_{1c} measurements, blood pressure, cholesterol, smoking, microalbuminuria testing, or screening for foot pulses recorded. Thirty-eight percent of patients with type 2 diabetes on medication had an HbA_{1c} above 7.5%. Compared with those on medication, patients treated by diet only were more likely to have raised blood pressure and less likely to be on antihypertensive medication. They were 45% more likely to have raised serum cholesterol levels and less likely to be prescribed lipid-lowering medication.

The success of a treatment strategy depends both on the patient's ability or will to adhere to the treatment prescribed as well as possible physician barriers against the treatment. Studies have shown that only 50 to 70% of the prescribed medication is actually taken by patients (262; 263). Furthermore, it has been clearly demonstrated that poor adherers are much more likely to have a bad outcome whether they are taking active study medication or placebo (264). Several factors are believed to be important for drug adherence. Many of the therapies given in an intensified multifactorial intervention ap-

proach are given as preventive treatments irrespective of the presence of symptoms, and therefore patients without symptoms may find, that the treatment may interfere more with daily life than the disease itself. In this respect, it is worth noticing, that patients may find that a change in lifestyle can lead to a large reduction in the quality of life and thus be a larger barrier for adherence to treatment than taking drugs (262). Even in case of symptoms, the start of a treatment may not relieve these, thereby in itself being a risk factor for non-adherence to treatment (265). However, another study did not find an association between relief of symptoms and adherence to treatment in a follow-up study for four years of more than 2,000 patients (266). The complexity of the drug regimen does also seem to be of importance, especially the number of dosages per day with decreased adherence the higher the number of dosages (267-269). Of course, side effects including drug interactions will also influence drug adherence, and finally cost of treatment may also be of importance. These issues will be discussed later. None of the three multiple risk factor intervention studies discussed had standardised measurements for adherence to treatment. The number and doses of drugs taken in each of the studies were by self-report by the patients.

In the Steno-2 study all patients in the intensive group were prescribed ACE inhibitors or angiotensin II receptor antagonists as well as a vitamin-mineral supplement which was delivered for free to the patients. While 97% of patients reported to take the ACE inhibitor or angiotensin II receptor antagonist at the eight year examination only 63% of patients reported to take the vitamin-mineral supplement. This shows that even within the same study group different barriers exist to different types of treatments. Clearly, the answer to question d) is that there indeed are major problems with adherence to both lifestyle and drug treatment in patients with type 2 diabetes. Further studies investigating solutions to these problems are warranted. Until these studies are available every effort must be made by health care personnel to make patients adherent to treatment according to current guidelines. One of the obstacles may be, that some physicians still think of type 2 diabetes as a relatively benign disease (270). It has been shown that physician barriers in following guidelines are related to the physicians knowledge of the disease (271). Fortunately, information to physicians about the disease can optimise the treatment of risk factors, as it has been demonstrated at the level of general practitioners (25; 258; 260).

Apart from being an obvious barrier to drug adherence side effects may cause serious health problems to patients. The magnitude of side effects of new drugs is investigated as part of the registration procedure, and furthermore most of the drugs mentioned in previous chapters have been investigated in single risk factor intervention trials. However, use of polypharmacy with several possible drug interactions has not been examined to a similar extend. One of the interactions that have been debated is the use of acetylsalicylic acid and ACE inhibitors, which is quite common in the treatment of type 2 diabetes. Some studies have suggested, that the beneficial effects of ACE inhibitors in reducing cardiovascular disease is diminished in patients taking acetylsalicylic acid (272), and also the combination of statin treatment and clopidogrel given as secondary prevention following a myocardial infarction and have been reported to weaken platelet inhibition (273). Even though these interactions may not play an important role at the clinical level, it does stress the importance of thorough investigation of side effects and drug interactions in patients treated with polypharmacy. Another example of concern is from the treatment of dyslipidaemia where beneficial treatment effects of both fibrates and statins have been demonstrated in single risk factor intervention trials. Yet, the combination of these two drug classes is not recommended, and recently one statin (cerivastatin) was withdrawn from the market because of fatal side effects when used in combination with a fibrate (274).

None of the six studies investigating the effect of intensified polypharmacological treatment in type 2 diabetes reported detailed information about drug interactions and side effects, and as a consequence our knowledge on this area is sparse. Further studies in this area are definitely required, although it is impossible to investigate all the possible drug combinations prescribed to patients with type 2 diabetes. This makes it, however, even more important with cautious follow-up of patients whenever new drugs are prescribed. One of the common side effects to treatment of hyperglycaemia in single risk factor trials is weight gain. It is noteworthy, that all six multiple risk factor intervention trials in type 2 diabetes found, that weight gain was, although expected, not significantly more pronounced with intensive than with conventional therapy. Similarly, hypoglycaemia was not more frequent with intensified multifactorial intervention compared to the control groups, although blood glucose levels were significantly lower with intensive therapy in all six studies.

The question of cost of treatment is also important, but results on this subject have not been published from the aforementioned multifactorial intervention studies in type 2 diabetes. The direct cost of drugs for the patient can definitely be a barrier for adherence to treatment (275). In Denmark reimbursement rules (year 2005) ensure that the direct cost of drugs cannot exceed DKK 3,805 per year (€510). However, the cost of remedies and strips for blood glucose measurements, foot care, healthy food etc. are not included in this amount, since special reimbursement rules exist within this field. In the Steno-2 study all insulin treated patients in the intensive group were urged to measure blood glucose at least once daily in order to adjust insulin dose. Yet, patients' costs are only a fraction of the total cost. The total costs for an average Danish patient with type 2 diabetes have been estimated from Aarhus County based on a scenario, where most patients are followed at the level of GPs with an average of 3.6 consultations per year (276). These figures show that the typical patient is not treated according to current guidelines since for example the average numbers of eye examinations, consultations at a chiropodist, home blood glucose measurements, monitoring of UAER, and measurement of blood lipids are much lower than recommended. Similarly, one third of patients are not treated with glucose lowering drugs, and only 14% percent of patients are receiving cholesterol-lowering drugs. Despite this the total cost is estimated to €750 with €175 spent on health care personnel, €460 spent on drugs, and €115 spent on remedies and analyses. Although the cost-effectiveness of multifactorial intervention in patients with newly diagnosed type 2 diabetes has not been evaluated, the cost-effectiveness of single risk factor intervention against hyperglycaemia (277; 278), hypertension (279), and dyslipidaemia has been demonstrated in patients with type 2 diabetes (280; 281).

To summarise this issue, our current knowledge does not support an unrestricted use of intensified multifactorial intervention in type 2 diabetes if economic factors are considered a major issue. In contrast, the use of an intensified multifactorial approach may prove highly cost-effective in high risk populations, e.g. in type 2 diabetic patients with elevated albumin excretion rate, or with known cardiovascular disorders.

9. AN ATTEMPT TO ESTIMATE THE STRONGEST COMPONENT OF THE INTENSIVE MULTIFACTORIAL INTERVENTION IN REDUCING RISK OF CARDIOVASCULAR DISEASE

Treatment guidelines for primary prevention of CVD in primary care use absolute risk, alone or in conjunction with relative risk. In order to determine optimal care it is desirable that all diabetic patients have their absolute CVD risk evaluated. International health authorities, e.g. The British National Service Framework (NSF), recommend application of the widely used Framingham equation to identify high risk patients. This equation was derived from a logistic regression equation of the CVD risk profiles of 5,573 subjects, mean age 30 years, initially free of CVD who were followed up for 12 years. The prevalence of diabetes in the cohort was about 5%.

There has been some debate regarding the accuracy of the Fram-

ingham equation to predict CVD event risk in patients with diabetes mellitus. This is illustrated by performing a risk analysis entering appropriate variables in the equation for the non-diabetic patients in the placebo arm of the West of Scotland Coronary Prevention Study (WOSCOPS) (282). In 3,293 placebo-treated patients, of whom 99% had no diabetes, the annual CVD event and mortality rates predicted by the Framingham risk function were 1.9% and 0.3%, compared with observed rates of 1.8% and 0.4%, respectively.

Using mean values for age, gender, systolic blood pressure, smoking habit, diabetes status, serum levels of total cholesterol and HDL-cholesterol, and assuming absence of left ventricular hypertrophy it is possible to estimate the predicted mean CVD event and mortality rates for diabetic patients recruited into the UKPDS (193). In 3,867 UKPDS patients the Framingham risk function predicted a mean annual CVD event rate of 1.6% and a CVD mortality rate of 0.2%, whereas observed rates were 2.7% and 1.0%, respectively. The Framingham risk function therefore appears to underestimate CVD event rates by 40% and CVD mortality by 80% in the UKPDS.

Recently, a newer risk calculator called the UKPDS Risk Engine based on data from the UKPDS was published (283). Whereas the Framingham model uses a dichotomous variable for glycaemia, i.e. presence or absences of diabetes, the UKPDS Risk Engine includes HbA_{1c} as a continuous variable. Furthermore, age as a risk factor is replaced by two diabetes-specific variables: age at diagnosis of diabetes and time since diagnosis of diabetes, as previous UKPDS analyses have shown the importance of this distinction to diabetic complications. The model provides risk estimates and 95% confidence intervals for non-fatal and fatal coronary heart disease, fatal coronary heart disease, non-fatal and fatal stroke, and fatal stroke. These can be calculated for any given duration of type 2 diabetes based on current age, gender, ethnicity, smoking status, presence or absence of atrial fibrillation and levels of HbA_{1c}, systolic blood pressure, and fasting serum levels of total cholesterol and HDL-cholesterol.

Both the Framingham and the UKPDS equations can be used on data from the Steno-2 sample in an attempt to estimate the strongest component of the "therapeutic package" in reducing the risk for CVD as defined by the various equations. Average risk factor profiles for patients in the intensive therapy group at baseline and at the end of the study have been calculated, thus giving an opportunity to differentiate the cardiovascular risk reduction into each of the entered variables. Furthermore, this has been done for each of the two treatment groups in the study. The baseline 10 year risk for CVD in the intensive therapy group in the Steno-2 study was 22% compared to 26% in the conventional therapy group using the Framingham equation, with the UKPDS Risk Engine giving almost identical results with 22% and 25%, respectively. The absolute risk for the combined endpoint in the Steno-2 study (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, amputations, invasive cardiovascular procedures, peripheral vascular procedures) was 24% in the intensive group and 44% in the conventional group, respectively. Excluding peripheral vascular procedures and amputations in order to make the definition of CVD in the Steno-2 study more comparable to the Framingham and UKPDS definitions reveals a much lower rate of 14% and 29%, respectively, during the follow-up period of 7.8 years, but still higher than predicted from both the Framingham and UKPDS equations for the conventional therapy group once again emphasizing that type 2 diabetic patients with microalbuminuria are high risk patients.

By entering the actual values at the end of follow-up and adjusting for the increase in risk by the increased age during follow-up the calculated event rates in both the intensive and conventional therapy group were higher than the observed event rates during follow-up in both models. The relative importance of each of the risk factors in the obtained risk reductions can then be calculated by entering one risk factor at a time. As shown in Figure 5 changes in serum lipids seem to account for the majority of the treatment effect in the Steno-2 study, both for the primary composite endpoint of CVD as

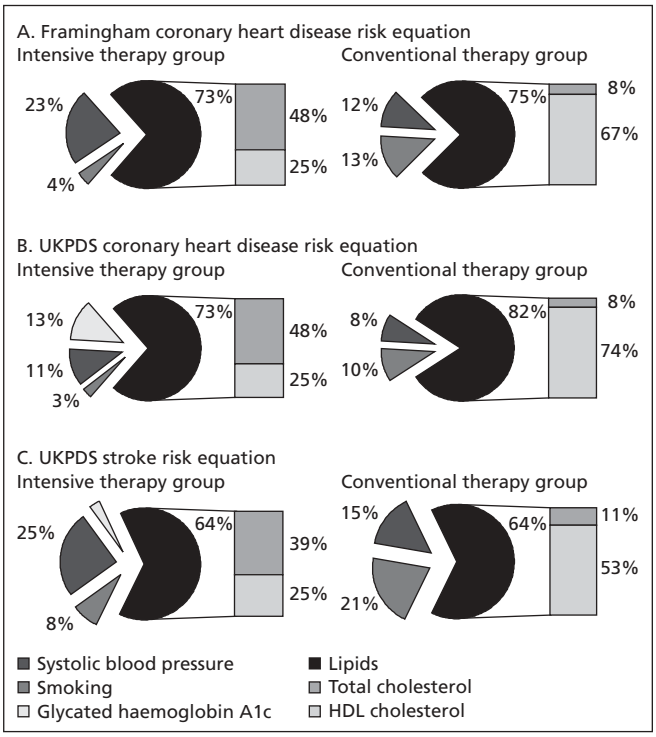


Figure 5. Both the Framingham and the UKPDS equations can be used on data from the Steno-2 cohort in an attempt to calculate the strongest component of the multiple risk factor intervention in reducing the risk for CVD in both treatment groups.

well as for stroke, whereas treatment of hyperglycaemia only seems to play a minor role. This is an intriguing finding, yet the consistency of the finding in both treatment groups for both coronary heart disease and stroke seems quite clear. The result for stroke is in accordance with results from the HPS, where serum total cholesterol was demonstrated to be an important intervention target in the prevention of stroke since treatment with 40 mg of simvastatin reduced the relative risk of stroke with 24% in patients with diabetes enrolled in the study (284). However, caution should be exercised in interpreting the results. Another explanation for the poor impact of blood pressure and glucose lowering therapy could be the simple fact that only 15% and 50% of patients in the intensive group reached the goals for glucose and blood pressure lowering therapy, respectively. Had these results been better the impact of the different interventions might have changed completely. Yet again, the results from the Steno-2 study might very well resemble every day clinical practice, especially for glucose lowering therapy.

10. THE RATE OF LATE COMPLICATIONS IS STILL FAR TOO HIGH IN INTENSIVELY TREATED TYPE 2 DIABETIC PATIENTS: ROOM FOR FUTURE IMPROVEMENTS

The cardiovascular complications are by far the most threatening for the long-term prognosis in patients with overt type 2 diabetes, and the high risk microalbuminuric patients participating in the standard multitargeted intervention in the Steno-2 study showed an event rate of the combined cardiovascular endpoint of 7% per year. Although the intensified multifactorial intervention cut this event rate by half, it is still more than three times as high as in the matched background population, leaving much room for improvements.

Lack of organisation in implementing guidelines at the primary care physician level seems to be a major problem in this respect (261), since clinical studies have demonstrated that proper organisation improves patients' risk profile and reduces complications also at a primary care level (25; 258; 260). Closer contact between specialists and general practitioners with the patient being the key person and messenger is a possible solution, but also the establishment of more specialised diabetes clinics may offer a solution to this problem.

Another radical fight back is obviously to intensify the primary prevention of type 2 diabetes (285-287). Perhaps a breakthrough in our understanding of the molecular pathogenesis of abdominal obesity, and thereby of targets for antiobesity drug development, will answer many of the current shortcomings in the prevention and successful treatment of the majority of type 2 diabetic patients, because abdominal obesity is known to cause insulin resistance and an atherogenic low-grade inflammatory state partially due to an excessive secretion of proinflammatory adipokines, including tumor necrosis factor-α (288).

Another target for major improvement is the treatment resistant hyperglycaemia of type 2 diabetic patients. The UKPDS showed a steady decline in pancreatic β-cell function with diabetes duration, most likely caused by an accelerated apoptosis induced by numerous factors, including chronic exposure to elevated levels of free fatty acids, glucose, and proinflammatory cytokines (289). Any intervention that might prevent β-cell apoptosis is expected to improve glycaemic regulation, as are treatments, (e.g., glitazones) that diminish insulin resistance and inflammation.

Treatment targets for serum levels of LDL-cholesterol and triglycerides can in most cases be achieved rather easily with statins and fibrates. In contrast, it is much more difficult to eliminate the low serum level of HDL-cholesterol as a cardiovascular risk factor. Also, to prevent cardiovascular complications, patients with diabetes might consider to eat fatty fish and walnuts (high in ω-3 fatty acids) several times a week (primary prevention of cardiovascular disorders), and patients with overt CVD (secondary prevention) or autonomic neuropathy might benefit from following current guidelines from the American Heart Association recommending daily supplements of 1 g ω-3 fatty acids (290). However, a recent Cochrane review questions this recommendation (291).

Although there is evidence from epidemiological studies that elevated serum levels of homocysteine (292) and proBNP (293) are strong predictors of increased risk of cardiovascular morbidity and mortality, there is still no convincing evidence from interventional trials that lowering these risk markers (e.g., homocysteine with folic acid) will improve long-term outcome in patients with type 2 diabetes (294).

Continued smoking has disastrous effects on the progression of retinopathy and cardiovascular complications, and much more needs to be explored about how to successfully apply smoking cessation approaches.

Finally, it is anticipated that progress within the field of pharmacogenomics, identifying by genotype those patients who are responders and less responders to a given drug treatment of hyperglycaemia, dyslipidaemia, or hypertension, will greatly contribute to efficacious personalised interventions to improve the risk marker profile and thereby enhance the health of patients suffering from type 2 diabetes.

11. APPENDIX

APPENDIX 1

Definitions of endpoints used in the Steno-2 study. An independent, masked endpoint committee consisting of two specialists in cardiology and one specialist in diabetology evaluated all cases and classified cardiovascular events into the following categories:

1.0 Cardiovascular death

1.1 *Sudden death:* Sudden death presumed to be due to ischaemic cardiovascular disease, occurring within 24 hours of the onset of symptoms without confirmation of cardiovascular disease, and without clinical or post mortem evidence of other aetiology.

1.2 *Fatal myocardial infarction:* death within 7 days of the onset of documented myocardial infarction (see 2.0).

1.3 *Congestive heart failure:* death due to clinical, radiological or post mortem evidence of congestive heart failure without clinical or post mortem evidence of an acute ischaemic event (which should then be coded as the cause). Cardiogenic shock to be included.

1.4 *Post cardiovascular invasive interventions:* death associated with the intervention: within 30 days of cardiovascular surgery, or within 7 days of cardiac catheterisation, or angioplasty, atherectomy, stent deployment or other invasive coronary or peripheral vascular interventions.

1.5 *Documented arrhythmia:* death due to bradyarrhythmias or tachyarrhythmias not induced by an acute ischaemic heart disease event (which should then be coded as the cause).

1.6 *Death following non-cardiovascular surgery:* death due to cardiovascular causes as defined in 1.1-1.5 and 1.7-1.8 and within 30 days of surgery.

1.7 *Fatal stroke:* death due to stroke occurring within 7 days of the signs and symptoms of a stroke.

1.8 *Other cardiovascular diseases:* death due to other vascular diseases including pulmonary emboli, and abdominal aortic aneurysm rupture.

1.9 *Presumed cardiovascular death:* suspicion of cardiovascular death with clinically supporting evidence which may not fulfil criteria otherwise stated. Example: Patient admitted with typical chest pain of 3 hours duration and treated as a myocardial infarction, but without ECG and enzymatic documentation to meet normal criteria.

2.0 Myocardial infarction (MI)

2.1 *Q-wave MI:* in comparison to the last ECG, presence of at least one new significant Q-wave on the standard 12-lead ECG as described in the Minnesota Code, and at least one of:

1. Typical symptoms (e.g. typical ischaemic chest pain lasting more than 30 minutes and/or
2. Significant elevation of serum enzymes – presence of any of the following criteria:
   a) elevation of troponine to above the upper limit of normal for the laboratory that performed the test
   b) elevation of creatine kinase MB (CK-MB) to twice the upper limit of normal for the laboratory that performed the test
   c) elevation of total CK to at least twice the upper limit of normal for the laboratory that performed the test
   d) elevation of aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), lactate dehydrogenase (LDH) to at least twice the upper limit of normal for the laboratory that performed the test with a characteristic pattern.

2.2 Non Q-wave MI: defined as a significant elevation of cardiac enzymes (at least twice the upper limit of normal) with or

without characteristic pain in absence of new significant Q-wave.

2.3 Probable non Q-wave MI: presence of new and persistent ST-T changes (more than 24 hours in duration) on the ECG with characteristic symptoms of ischaemic chest pain without documentation of enzyme elevation.

2.4 Silent MI: development of new significant Q waves on the ECG (Minnesota Code) in at least two adjacent leads in the absence of any other evidence of myocardial infarction (in this case the date of event will be assessed as halfway between the date of discovery and last normal ECG).

2.5 Non-fatal MI post cardiovascular invasive interventions: MI (as defined in 2.1, 2.2, 2.3 or 2.4) associated with the intervention within 30 days of cardiovascular surgery, or within 7 days of cardiac catheterisation, or angioplasty, atherectomy, stent deployment or other invasive coronary or peripheral vascular interventions.

2.6 Non-fatal MI post non-cardiovascular surgery: MI (as defined in 2.1, 2.2, 2.3 or 2.4) occurring within 30 days of non-cardiovascular surgery.

3.0 Stroke

3.1 Definite ischaemic stroke: a CT or MRI scan within 2 weeks of onset of a definite stroke (focal neurological deficit greater than 24 hours) with evidence of infarction, or autopsy confirmation.

3.2 Definite haemorrhagic stroke (primary intracerebral, subarachnoid, or secondary to cerebral infarction): confirmation with a CT or MRI scan within 2 weeks of stroke, or at autopsy or by lumbar puncture.

3.3 Stroke of unknown aetiology: definite stroke of unknown aetiology when CT, MRI or autopsy are not done, or where CT or MRI scan does not reveal pathology.

3.4 Non-fatal stroke post cardiovascular invasive interventions: stroke (as defined in 3.1, 3.2 or 3.3) associated to the intervention within 30 days of cardiovascular surgery, or within 7 days of cardiac catheterisation, or angioplasty, atherectomy, stent deployment or other invasive coronary or peripheral vascular interventions.

3.5 Non-fatal stroke post non-cardiovascular surgery: stroke (as defined in 3.1, 3.2 or 3.3) occurring within 30 days of non-cardiovascular surgery.

4.0 Transient ischaemic attacks (TIA)

4.1 Definite TIA: focal neurological deficits with duration of less than 24 hours. Deficits must be observed and described by a physician.

4.2 ProbableTIA: focal neurological deficits with duration of less than 24 hours. Deficits not observed or described by a physician.

4.3 TIA post cardiovascular invasive interventions: TIA (as defined in 4.1 or 4.2) associated to the intervention within 30 days of cardiovascular surgery, or within 7 days of cardiac catheterisation, or angioplasty, atherectomy, stent deployment or other invasive coronary or peripheral vascular interventions.

4.4 TIA post non-cardiovascular surgery: TIA (as defined in 4.1 or 4.2) occurring within 30 days of non-cardiovascular surgery.

5.0 Amputation (includes both amputation and exarticulation)

5.1 Amputation caused by cardiovascular disease

5.2 Amputation caused by pressure wound/gangrene/infection

6.0 Invasive cardiovascular procedures

6.1 Coronar artery bypass graft (CABG)

6.2 Percutaneous transluminal coronary angioplasty (PTCA)

6.3 Attempted PTCA: (to be used in case of an unsuccessful attempt)

6.4 Coronary stent deployment

6.5 Coronary arteriography with stenosis

7.0 Peripheral vascular procedures

7.1 Bypass surgery: state localisation
- 7.1.1 lower extremity
- 7.1.2 upper extremity
- 7.1.3 carotid

7.2 Percutaneous transluminal angioplasty (PTA): state localisation
- 7.2.1 lower extremity
- 7.2.2 upper extremity
- 7.2.3 carotid

7.3 Attempted PTA: (to be used in case of an unsuccessful attempt). state localisation
- 7.3.1 lower extremity
- 7.3.2 upper extremity
- 7.3.3 carotid

7.4 Stent deployment: state localisation
- 7.4.1 lower extremity
- 7.4.2 upper extremity
- 7.4.3 carotid

7.5 Thrombendarterectomy/thrombectomy: state localisation
- 7.5.1 lower extremity
- 7.5.2 upper extremity
- 7.5.3 carotid

7.6 Stenosis in a. carotis: verified by arteriography or Doppler ultrasound

8.0 Death from other than cardiovascular cause

8.1 cancer

8.2 suicide

8.3 hypoglycaemia

8.4 accident

8.5 unspecified

9.0 Ischaemia in ECG

9.1 Ischaemia in resting ECG: Minnesota code 1.1-1.3, 4.1-4.4, 5.1-5.8 or 7.1

9.2 Ischaemia in work load ECG: ST-depression of more than 1 mm in any lead

10.0 Distal blood pressure gradient

Significant decline in distal blood pressure gradient: decline in systolic blood pressure gradient of at least 28 mm Hg between the right arm and great toe in one or both legs.

APENDIX 2

Framingham 10 year risk score charts for men and women. Aspirin therapy as primary prevention should be considered of the 10 year risk score exceeds 6% (248). To convert values for cholesterol to millimoles per liter, multiply by 0.02586 Box 1 and Box 2.

Continues next page.

Estimate of 10 Year Risk for Men (Framingham Point Scores)

Age	Points
20-34	–9
35-39	–4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Total cholesterol (mg/dl)	Points				
	Age: 20-39	40-49	50-59	60-69	70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200–239	7	5	3	1	0
240-279	9	6	4	2	1
≥280	11	8	5	3	1

	Points				
	Age: 20-39	40-49	50-59	60-69	70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL (mg/dl)	Points
≥60	–1
50-59	0
40-49	1
<40	2

Systolic BP (mm Hg)	Points	
	If untreated	If treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

	Point total	10-Year risk %
	<0	<1
	0	1
	1	1
	2	1
	3	1
	4	1
	5	2
	6	2
	7	3
	8	4
	9	5
	10	6
	11	8
	12	10
	13	12
	14	16
	15	20
	16	25
10 Year risk %	≥17	≥30

Estimate of 10 Year Risk for Women (Framingham Point Scores)

Age	Points
20-34	–7
35-39	–3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

Total cholesterol (mg/dl)	Points				
	Age: 20-39	40-49	50-59	60-69	70-79
<160	0	0	0	0	0
160-199	4	3	2	1	1
200–239	8	6	4	2	1
240-279	11	8	5	3	2
≥280	13	10	7	4	2

	Points				
	Age: 20-39	40-49	50-59	60-69	70-79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL (mg/dl)	Points
≥60	–1
50-59	0
40-49	1
<40	2

Systolic BP (mm Hg)	Points	
	If untreated	If treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
≥160	4	6

	Point total	10-Year risk %
	<9	<1
	9	1
	10	1
	11	1
	12	1
	13	2
	14	2
	15	3
	16	4
	17	5
	18	6
	19	8
	20	11
	21	14
	22	17
	23	22
	24	27
	≥25	≥30
10 Year risk %		

ABBREVIATIONS

ACE: Angiotensin converting enzyme
ALAT: Alanine aminotransferase
ASA: Acetylsalicylic acid
ASAT: Aspartate aminotransferase
BMI: Body mass index
CK: Creatine kinase
CVD: Cardiovascular disease
CHD: Coronary heart disease
ECG: Electrocardiogram
ESRD: End stage renal disease
GFR: Glomerular filtration rate
GP: General practitioner
HbA_{1c}: Glycosylated haemoglobin A1c
HDL: High density lipoprotein
HPLC: High performance liquid chromatography
LDH: Lactate dehydrogenase
LDL: Low density lipoprotein
NPH: Neutral protamine Hagedorn
NT-proBNP: N-terminal proBrain Natriuretic Peptide
PROBE: Prospective randomised open blinded endpoint
TER_{alb}: Transcapillary escape rate of albumin
UAER: Urinary albumin excretion rate
UKPDS: United Kingdom Prospective Diabetes Study
vWF: Von Willebrand factor

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