TYPE 2 DIABETES
Health Technology Assessment of screening, diagnosis and treatment

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Health Technology Assessment of screening, diagnosis and treatment
This report is an English translation of a Danish HTA report published by DACEHTA in the autumn of 2003.

Type 2 diabetes will become one of the greatest challenges facing the Danish health service in the coming years.

A total of between 200,000 and 300,000 Danes suffer from the disease. Of these, approximately half are unaware of the fact. In addition, growth in the number of patients with Type 2 diabetes is increasing. Diabetes itself can cause troublesome symptoms, but the main reason that diabetes is a major and costly disease for society is that the disease can lead to a number of diabetic complications that can have very serious consequences for the patient’s state of health in the long term.

It is for these reasons among others that the present broad health technology assessment of Type 2 diabetes has been carried out.

In order to provide a comprehensive basis for decisions, the report integrates systematic assessments of concrete interventions with health economic analyses and analyses of the consequences for patients and organisation in the diabetes area. The report has undergone peer review among external Scandinavian experts.

DACEHTA hopes that the report will comprise a significant contribution to decision making about future efforts to deal with Type 2 diabetes in Denmark.

A well-functioning organisation at both the patient level and regional level can be decisive in determining whether potential health benefits can be attained.

The report is thus directed at decision makers responsible for planning an overall strategy for case finding, diagnosis and treatment of Type 2 diabetes. In addition, the report is directed at the professional groups responsible for the daily care of patients with Type 2 diabetes, as well as at patients, patient associations and others interested in the area.

DACEHTA would like to thank all members of the Project Group as well as others who have contributed to the report for the considerable work that has been carried out since the start of the project.

Danish Centre for Evaluation and Health Technology Assessment
May 2005

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Director
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The report has been prepared by a cross-disciplinary Project Group comprised of four subgroups each with their own chairman and theme. Each individual subgroup has been responsible for drawing up their respective contributions to the report. These have been collated and edited by an editorial committee consisting of the Chairman of the Project Group, the Scientific Secretary and DACEHTA’s Project Leader – in collaboration with the Subgroup Chairmen and the other members of the Project Group.

The report consists of 8 chapters and 11 annexes.

- The report starts with a short presentation of the main conclusions and recommendations.
- Thereafter follows a more in-depth summary containing all the report’s conclusions and recommendations.
- Chapter 1 describes the background and aims of the project and the methods employed when preparing the report. The method section is supplemented by Annex 1 and Annex 2, as well as by an insert to the report that briefly describes the literature search process and the table upon which evidence grading of the literature and grading of the report’s recommendations are based. The chapter closes with a description of the natural history of Type 2 diabetes, including differentiation between Type 1 and Type 2 diabetes.
- Chapter 2 assesses various methods for diagnosing Type 2 diabetes and describes their suitability under various organisational frameworks – in outpatient clinics and in general practice.
- Chapter 3 assesses various screening strategies and the appropriateness of introducing a population-based screening programme for Type 2 diabetes compared with other case finding strategies.
- Chapter 4 examines and assesses a number of important interventions that share the common feature that they do not include the direct intake of drugs. The main topics are diet and overweight, self-monitoring of blood glucose, exercise, smoking, education, shared care and non-pharmacological treatment of the diabetic foot.
- Chapter 5 assesses various pharmacological interventions against risk factors for Type 2 diabetes. One of the main topics focussed on is polypharmacological treatment in which patients are treated with several drugs against several risk factors.
- Chapter 6 assesses screening for various late complications of Type 2 diabetes. These are diabetic retinopathy, nephropathy/hypertension, neuropathy, foot complications and diabetic cardiovascular disease.
- Chapter 7 discusses various strategies for monitoring and registration in the diabetes area.
- Chapter 8 briefly examines the perspectives entailed by the most important studies pertaining to primary prevention of Type 2 diabetes.
Glossary

**Abdominal obesity** – apple-shaped obesity.

**ADA** – American Diabetes Association.

**Albumin/creatinine ratio** – ratio of albumin to creatinine in the urine. Used as a more precise indicator of the level of albumin excretion in the urine.

**Albuminuria** – excretion of albumin in the urine. A distinction is drawn between normo-albuminuria, microalbuminuria and macroalbuminuria.

**AMI** – acute myocardial infarction.

**Angina pectoris** – heart pain caused by atherosclerosis of the coronary arteries.

**Angiopathy** – disease of the blood vessels. A distinction is typically drawn between microangiopathy, which is disease of the small blood vessels, and macroangiopathy, which is disease of the large blood vessels.

**Anticoagulation** – treatment to prevent blood clot formation.

**Antioxidants** – substances that hinder undesirable oxidation of various substances in the body.

**Apoplexy** – stroke or infarct/haemorrhage in the brain.

**Asymptomatic** – devoid of symptoms of a given disease.

**Bias** – prejudice, partiality, skewness. A process in the planning, implementation or analysis phases of a study that tends to lead to results or conclusions that systematically deviate from the truth. Bias is counteracted by “blinding” of investigators and patients.

**Biothesiometer** – device for measuring vibration perception threshold.

**BMI/Body Mass Index** – unit for describing the relationship between height and weight. Calculated as weight (kg)/(height (metre))^2. The upper limit for normal BMI is 25.

**Cardiovascular death** – death caused by atherosclerosis of the blood vessels in the heart.

**Charcot foot** – A deformed foot that develops after degeneration of the skeletal architecture of the foot.

**CI** – confidence interval – the interval that describes the uncertainty with which a mean value is determined.

**Clinical case finding** – identification of patients with undetected diabetes, patients who either present with symptoms of the disease or patients who have states associated with diabetes.

**Cohort** – a defined group of individuals with something in common, for example born within a given period of time, that is followed for a set number of years with regard to some condition or other. Can be prospective or retrospective (see these terms).

**Compliance** – willingness, for example the patient’s willingness to take medicine or follow instructions.

**Diabetes schools** – places where diabetes patients can receive education in their disease.

**Dyslipidemia** – raised level of lipids in the blood and an unfavourable distribution between the various types of blood lipids.

**ECG** – electrocardiogram

**ED** – see erectile dysfunction.

**Erectile dysfunction** – lack of ability to achieve an erection.

**ESRF/End Stage Renal Failure** – kidney failure.

**Evidence-based medicine** – often abbreviated EBM – is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.

**FBG** – fasting blood glucose.

**FPG** – fasting plasma glucose.

**Fundus photography** – photography of the inner lining of the eye (fundus).

**Gastric banding** – surgical treatment of extreme obesity where the upper part of the stomach is reduced to a small stomach.

**Gestational diabetes** – diabetes arising during pregnancy.

**Glycaemic regulation** – an overall expression of how well the blood glucose level is regulated.

**Gold standard** – reference method for comparing diagnostic tests. The expression derives from the time when the currency standard was gold rather than the floating currencies of today.

**HbA1c** – long-term blood glucose that indicates the average glucose level over the preceding 2-3 months.

**HDL cholesterol** – high-density lipoprotein cholesterol – the good cholesterol.

**HTA** – Health technology assessment

**Hypertension** – raised blood pressure. The WHO defines hypertension as a blood pressure over 140/90.

**Hypocaloric diet** – diet that contains fewer calories than the body needs, i.e. a diet that will lead to weight loss.

**IDDM** – Insulin dependent diabetes mellitus – Type 1 diabetes.
IFG/Impaired Fasting Glycaemia – raised fasting blood glucose concentration that does not exceed the diagnostic limit for diabetes.

IGT/Impaired Glucose Tolerance – raised blood glucose concentration two hours after intake of a standard glucose solution, but one that does not exceed the diagnostic limit for diabetes.

Incidence – number of cases of a disease that arise during a given period (usually 1 year) in a specified population. Compare with prevalence.

Insulin – hormone formed by the beta cells in the pancreas. Insulin is necessary for the transport of glucose from the blood to the cells.

Insulin resistance – state in which the body’s cells do not react sufficiently to a given concentration of insulin in the organism.

LDL cholesterol – low-density lipoprotein cholesterol – the bad cholesterol.

Lipids in the blood – fatty substances in the blood.

Maculopathy (diabetic) – sight-threatening form of retinopathy in which the changes spread towards the central part of the retina and damage the central vision.

Meta analysis – An overview, which uses statistical methods to summarise the results of a number of independent investigations. Apart from the statistical analysis the meta analysis differs from the traditional review article in that data collection is based on a clearly defined protocol aimed at minimising bias, i.e. selection of the articles cited in the meta analysis is based on transparent criteria and does not just reflect for example the preferences of the author.

Monofilament – a short piece of nylon like a hairbrush bristle that typically bows at a pressure of 10 g and is used to test the sensitivity of nerves, primarily in the foot.

Monounsaturated lipid – lipid that is beneficial to the body.

Negative predictive value – often abbreviated NPV. The probability that a person is healthy if the test is negative. Compare with positive predictive value (PPV).

Nephropathy – kidney disease.

Neuropathy – disorders of the peripheral nerves.

NIDDM/Non insulin dependent diabetes mellitus – Type 2 diabetes.

NPR – National Patient Register.

Odds ratio – often abbreviated OR. Defines the ratio between having and not having a disease in a group exposed to a give risk factor.

OGTT – oral glucose tolerance test.

OHA – oral hypoglycaemic agents, tablets against raised blood glucose.

Ophthalmoscopy – examination of the eye using an ophthalmoscope.

OR – see odds ratio

Placebo – medically inert substance (typically chalk or the suchlike) that is used in connection with randomised trials.

Polypharmacological treatment/polypharmacy – concomitant pharmacological treatment of several risk factors with several different drugs.

Positive predictive value – often abbreviated PPV. The probability of having the disease if the test is positive. Compare with negative predictive value (NPV).

Prevalence – the proportion of a population that has a disease at a given point in time. Compare with incidence

Proliferative diabetic retinopathy – sight-threatening eye disease in which new blood vessels form in the retina.

QALY – see quality-adjusted life-year.

Quality-adjusted life-year – a measure of a person’s remaining life-years weighted with a health index.

RBG/Random blood glucose – blood glucose measured at a random time during the day.

RCT/randomised controlled clinical trial – rationally designed clinical trial aimed at investigating the effect of a treatment. In order to preclude subjective errors the trials are often carried out “double blind” such that neither the patient nor the physician knows whether the patient receives the test preparation or the control preparation. It is imperative that the treatments are allocated randomly among the treated groups.

Retinopathy (diabetic) – changes/lesions in the periphery of the retina caused by disturbances of the blood supply to the retina.

Retrospective – looking towards the past.

RR – relative risk reduction.

Screening – an investigation of a presumably healthy group of persons aimed at identifying persons having a high risk of developing a given disease or identifying persons with early stages of the disease.

Sensitivity – the probability of testing positive given that one has the disease. The proportion of people with the disease who are detected by a given test/screening. Compare with specificity.
Specificity – the probability of testing negative given that one is healthy. Compare with sensitivity.

TCI – Transient cerebral ischaemia.

Vitrectomy – the surgical removal of all or part of the vitreous body i.e. the transparent gel that fills the eye from the iris to the retina.

VLCD/Very Low Calorie Diet – very strict diet whose calorie content is approx. 800 calories/day.

WHO – World Health Organisation.
1 Introduction

1.1 Background for the project

In October 1999, the Parliamentary Committee on Health requested the Minister for Health to respond to an enquiry from the Danish Diabetes Association concerning the increasing number of patients with adult onset diabetes. In his preliminary response, the Minister pointed out that in addition to the scientific documentation for interventions it was important to clarify a number of aspects – including organisational, personnel and ethical aspects. In his final response, the Minister informed the Parliamentary Committee on Health that the Danish Institute for Health Technology Assessment (Now the Danish Centre for Evaluation and Health Technology Assessment) intended to investigate the possibilities for undertaking a regular HTA of case finding, diagnosis and treatment of Type 2 diabetes.

The Danish Institute for Health Technology Assessment, moreover, had received two applications concerning Type 2 diabetes for its 1999 HTA grants and, in view of the above, decided to summon these projects for preliminary discussions concerning a national HTA on Type 2 diabetes. These discussions among a wider circle of experts led to a decision in early 2000 to initiate a broad HTA project. In mid 2000, the Institute started to establish a cross-disciplinary Project Group.

The aim of the present report is to improve the foundation upon which the Counties and others can base overall decisions about diabetes care in Denmark.

The report is thus directed at decision makers responsible for planning an overall strategy for case finding, diagnosis and treatment of Type 2 diabetes. In addition, the report is directed at the professional groups responsible for the daily care of diabetes patients, as well as at patients, patient associations and others interested in the area.

1.2 Purpose and scope

The more than 20-person cross-disciplinary Project Group was assigned responsibility for planning a broad HTA of case finding, diagnosis and treatment of Type 2 diabetes. The task was to produce a broad, systematic and well-documented basis for decision making in order to clarify the preconditions for and consequences of well-defined, central interventions in the Type 2 diabetes area.

It is thus characteristic of this project that it was not instigated by the introduction of a new medical technology in the Danish health service, but instead by the marked growth in the number of patients with Type 2 diabetes and the expected major consequences this growth will have for public health and the Danish health service. It was therefore up to the Project Group’s experts in cooperation with the Danish Institute for Health Technology Assessment to more closely define the task by selecting the specific focus areas for the report.

The first meetings were thus primarily used for discussions on defining the task. After thorough consideration it was decided to focus the analysis on five main topics:

- Diagnosis in cases of suspected Type 2 diabetes
- Screening for Type 2 diabetes
- Non-pharmacological treatment of Type 2 diabetes
- Pharmacological treatment of Type 2 diabetes
- Diagnosis and screening for late complications of Type 2 diabetes.

Examination of these topics in the report is structured in separate chapters, each of which comprises a health technology assessment. The report can therefore be said to contain five HTAs that, if necessary, can be read independently of each other. Moreover, the last chapter on screening for late diabetic complications is subdivided into smaller analyses of screening for specific complications. Each chapter thus contains an examination of the documentation for the individual interventions as well as their patient-related, organisational and economic consequences.
That the HTA report examines prevention of Type 2 diabetes in a single section focusing only on the overall perspectives rather than through a more comprehensive analysis is due to the fact that there is already much existing knowledge on the significance of weight and exercise and a healthy diet in particular for preventing Type 2 diabetes. Moreover, with population-oriented initiatives it is difficult to discriminate between primary prevention aimed at one disease and interventions aimed at primary prevention of other lifestyle diseases. It would thus be inappropriate to focus on primary prevention of Type 2 diabetes without considering the initiatives in a wider perspective in relation to more general prevention of a number of related widespread diseases. The topic would then fall outside the scope of the present HTA project, however.

Treatment of late complications of diabetes was excluded as a focus area (in contrast to screening for late complications) as the Project Group found that the documentation for the usefulness of the treatment efforts directed at the known late complications of diabetes are generally well documented.

Finally, these exclusions should also be seen as an attempt to restrict the extent of the task which, even given the above exclusions, has been a continual challenge for the Project Group.

1.3 Methods

Systematic literature searches have been conducted for each of the HTA’s five main themes. In addition, some articles have been identified from reference lists in relevant reports and articles.

Brief summaries of the literature reports are presented in Annex 1. The actual literature reports with detailed descriptions of the search strategies and results can be ordered directly from the Danish Centre for Evaluation and Health Technology Assessment.

Evidence levels and recommendation grades

Evidence grading of the literature was based on “Levels of Evidence and Grades of Recommendation” drawn up by the National Health Service Research and Development Programme, Centre for Evidence-Based Medicine in Oxford, in 1998, cf. Annex 2, and the insert to this report. These were revised in 2001, cf. www.cebm.net/levelsofevidence.asp, but the changes do not affect the grading of evidence in the present report. The grading ranges from 1, which is the highest level of evidence, for example well-conducted meta-analyses of randomised controlled trials, to 5, which represents the lowest level of evidence, for example an expert assessment devoid of explicit critical evaluation. Based on this evidence grading, the derived recommendations are graded on a scale from A, the highest level, to D, the lowest level. Even though the literature on the health economics area was examined and assessed, evidence grading has not been carried out on the health economics studies and associated conclusions.

The evidence level is stated in bold typeface immediately following the individual reference in the text and following the conclusions in the various summaries and sub-conclusions. In cases where the evidence level is not stated, either the studies are qualitative or the issues are such that evidence grading is not considered relevant – for example in definitions. The recommendation grades are stated in conclusions and summaries.

1.4 What is Type 2 diabetes?

In summer 2000, a much discussed report on Type 2 diabetes and the metabolic syndrome was published in the Journal of the Danish Medical Association “Ugeskrift for Læger” (2). The report specified guidelines for the treatment of Type 2 diabetes and for many people has thus become the tool of choice when planning control and treatment of diabetes. The present HTA report can be seen as a follow-up to this report. Certain aspects, in particular the patient-related aspects of the disease and not least organisation and health economics, are described in much greater detail in the present report than in the guidelines report. Moreover, the HTA report is based on a systematic review and evaluation of the literature (see Section 1.3), whereas the guidelines report more reflects the knowledge and the opinions of the authors at the time of publication. This does not mean that the recommendations laid out in the guidelines report are no longer applicable, however.

Diabetes is rapidly advancing, and the number of patients is expected to increase markedly in the next few decades. In Denmark there are believed to be 100,000-150,000 diagnosed patients with Type 2 diabetes. The disease is often undiagnosed, and it is estimated that half of all Danes with the disease are unaware that they
have it such that the real number of cases is probably considerably higher (200,000-300,000). It is estimated that there are approx. 10,000-20,000 new cases each year.

Diabetes mellitus is characterised by raised blood glucose in both the fasting state and following a meal. The disease is diagnosed by measuring the glucose level in a blood sample taken either in the fasting state and/or after the person has consumed a standardised dose of sugar (called the oral glucose tolerance test or OGTT). The disease can also be diagnosed by demonstrating a markedly raised glucose level with concomitant presence of diabetes-related symptoms.

There are several different forms of diabetes mellitus. The two most frequent are Type 1 and Type 2 diabetes. This report exclusively concerns Type 2 diabetes mellitus, but experience from Type 1 diabetes is occasionally utilised in the report. Distinguishing between the two forms of diabetes does not usually pose any great problem. Type 1 diabetes mellitus (formerly termed insulin dependant diabetes mellitus (IDDM) or juvenile onset diabetes) is often diagnosed during childhood or the teenage years. The onset is relatively abrupt and usually occurs in slim or underweight persons. In contrast, Type 2 diabetes (formerly termed non insulin dependent diabetes mellitus (NIDDM) or adult onset diabetes) often develops in middle-aged and elderly persons. These are often overweight (especially abdominal obesity/apple-shaped obesity), often have Type 2 diabetes in the family, and onset of the disease is slower than in Type 1 diabetes. It should be mentioned, though, that it can occasionally be difficult to differentiate between the different types of diabetes in elderly persons (where Type 1 diabetes also occurs), and in these situations measurement of insulin production can be diagnostically useful (a blood sample): insulin production has ceased or is reduced in Type 1 diabetes patients, whereas insulin production is often raised in Type 2 diabetes patients, but is insufficiently effective (insulin resistance).

Type 2 diabetes is often not diagnosed until the patient seeks medical attention in connection with the development of diabetes-related symptoms such as thirst, excessive urination, fatigue, weight loss and infectious diseases. Similarly, the disease is not infrequently diagnosed in connection with the detection of diabetes-related complications such as myocardial infarct, stroke, and gangrene in the feet or with the detection of diabetic retinopathy. Patients have had diabetes for an estimated 6-10 years when the disease is diagnosed due to diabetes-related symptoms or after the detection of diabetic complications. Thus it has been found that up to 50% of the patients already have diabetes-related complications at the time of diagnosis.

Approx. 80% of the patients with Type 2 diabetes are overweight, and this probably plays a central role for the development of diabetes. The exact cause of the development of diabetes is unclear. However, a reduced sensitivity to insulin in the body (insulin resistance) is thought to play an important role for the development of the disease, especially in combination with reduced insulin secretion for the given insulin resistance. Insulin resistance can also precede diabetes. The increasing obesity in the population together with the decreasing level of physical activity and the growing population of elderly persons are seen as the predominant causes of the increasing frequency of diabetes in several different populations.

Diabetes can cause bothersome symptoms itself, but the main reason why diabetes is a widespread and costly disease is the fact that it can lead to diabetic complications. These complications are subdivided into microvascular complications and macrovascular complications or atherosclerosis. In this connection it is important to be aware that Type 2 diabetes is very frequently accompanied by other risk factors for the development of atherosclerosis. Thus in addition to raised glucose values, diabetes patients often also exhibit overweight (as mentioned above), hypertension and dyslipidemia. For this reason, Type 2 diabetes patients are often considered as having a syndrome with several concomitant risk factors for cardiovascular disease. The syndrome has been given the name “insulin resistance syndrome” or “the metabolic syndrome”.

Several studies have shown that changes in lifestyle through dietary change, increased physical activity and weight loss can hinder or delay the development of diabetes in persons at risk of developing Type 2 diabetes.

The treatment of Type 2 diabetes is mainly founded on these lifestyle modifications, but these are often insufficient to achieve the treatment objectives with respect to blood glucose values, weight, blood pressure and blood lipid levels. It is thus necessary to employ medication, which for many patients will mean treatment with a not insignificant number of tablets daily.

As is apparent from the above, Type 2 diabetes is a disease in which the participation of the patient in treatment and control is important. This self-care is a fundamental principle in diabetes treatment. It is thus...
essential that the patient acquires the “tools” necessary to be able to achieve satisfactory self-care. This requires that the patient is taught in several different disciplines, and that a well-established treatment system is available that the patient can use as needed.

Apart from the self-care carried out by the patient the treatment needs to be controlled by a professional therapist. The main elements of this consist of control of blood glucose and lipid levels, blood pressure and weight.

Blood glucose is measured in mmol/l. This only provides a snapshot of the state of disease, and only repeated measurements will enable the patient and therapist to evaluate the state of blood glucose regulation. Assessment of the blood glucose level over a longer period of time is therefore based on HbA1c or glycosylated haemoglobin, which measures the binding of glucose to haemoglobin in the blood. This value expresses the blood glucose level in the preceding approx. 8-12 weeks. Measuring this value every three months or so thus provides a rather precise impression of the average blood glucose over a period of time.

The lipid content of the blood is measured as total cholesterol, which consists of the favourable cholesterol (HDL cholesterol, best high) and the cholesterol that is detrimental (LDL cholesterol, best low). It is also usual to measure another lipid called triglyceride. In patients with Type 2 diabetes this lipid is associated with an enhanced risk of atherosclerosis.

Blood pressure is measured as the high (systolic) and low (diastolic) pressure, e.g. 140/80 mmHg. The systolic pressure indicates the expulsion pressure at the heart, while diastolic pressure indicates the pressure in the blood vessels when the heart begins to fill with blood after an expulsion.

As regards the microvascular diabetic complications, these are all preceded by an asymptomatic phase. All these complications can to a greater or lesser extent be prevented from arising (primary prevention) or from progressing further (secondary prevention).

The primary prevention consists of maintaining an as near normal blood glucose level as possible through exercise, diet, etc. In addition it is known that optimal control of blood pressure can prevent some of the complications.

The secondary prevention is initiated when the complication is diagnosed. This applies to diabetic retinopathy, diabetic nephropathy and diabetic neuropathy.

Diabetic retinopathy can develop into two sight-threatening forms. With proliferative diabetic retinopathy the disease primarily develops in the periphery of the retina, while diabetic maculopathy primarily develops around “the yellow spot” where the sharp vision is located. The two sight-threatening complications are not detected by the patient during the early stages, when they can be prevented by regulation of blood pressure and blood glucose and effectively treated by laser treatment. Consequently the patients should undergo regular screening by direct investigation (ophthalmoscopy) or photographic documentation (fundus photography) of the retina so that the changes can be detected in time. It is estimated that approx. 7% of all Type 2 diabetes patients are vision-impaired due to diabetes, and that approx. 1.5% are blind.

Diabetic nephropathy makes itself apparent through gradually increasing excretion of protein in the urine and gradually deteriorating renal function. The protein primarily used to assess the degree of excretion is albumin. The excretion can be measured in both a random urine sample and a morning urine sample, and in pooled night urine or pooled 24-hr urine. Irrespective of the way the urine is collected, the level of excretion is expressed in three phases from normal (normo-albuminuria), to incipient nephropathy (microalbuminuria) to manifest diabetic nephropathy (macroalbuminuria). The treatment of diabetic nephropathy aims particularly at normalisation of the blood pressure, but in the final stages of diabetic nephropathy dialysis can be necessary. Renal failure caused by Type 2 diabetes is thus becoming the most frequent reason for dialysis treatment (which is already the case in USA) due to the large number of patients with Type 2 diabetes. It is estimated that 4-8% of a Type 2 diabetes population will develop renal failure.

Diabetic neuropathy encompasses a much wider spectrum than the two preceding complications. The most important of the neuropathies is the one that is reflected in the loss of sensation, especially in the feet. This condition is difficult to treat and comprises a significant risk factor for subsequent development of foot ulcers that, in severe cases of infection, can necessitate amputation. Amputation can also be necessitated by a state
where neuropathy combined with atherosclerosis leads to foot ulcers and gangrene. More rare is painful neuropathy, which can cause the patient debilitating pains, especially in the legs. Finally, there are numerous symptoms that can be attributed to neuropathy in the so-called autonomic nerves, symptoms such as nausea, vomiting, sweats, dizziness, impotence, etc.

It can thus be concluded that Type 2 diabetes is a frequent disease and one that often exists in an undetected form. Patients with Type 2 diabetes have a considerable morbidity and excess mortality from their disease, especially due to atherosclerosis. Scientific evidence exists that it is possible to reduce the risk of diabetic complications. In the early stages these complications do not exhibit symptoms and hence can beneficially be detected through screening procedures since the complications per se can be treated, thereby reducing the risk of a debilitating condition.
2 Diagnosis upon suspicion of Type 2 diabetes

Type 2 diabetes is a frequent chronic disease, and the latest Danish epidemiological study by the Copenhagen County Centre for Disease Prevention and the Steno Diabetes Center (3) shows that there are between 200,000 and 300,000 persons with Type 2 diabetes in Denmark. Of these, approximately half have the disease without knowing it (without the diagnosis diabetes having been made). The number of new (incident) cases each year is unknown, but with an expected mean lifetime of 15-20 years after diagnosis is made, 10,000 to 20,000 new cases of diabetes will arise each year. Danish and foreign studies show that approx. 7% of the total health service budget is used on the treatment of diabetes and complications affecting the eyes, kidneys and cardiovascular system (4, 5) (3b).

A significant hurdle in relation to case finding and diagnosis is that the diagnosis can be made using several different procedures and measurement methods, and that early diagnosis is hampered by the fact that symptoms of the disease are very vague or absent the first few years. This chapter solely assesses matters related to the diagnosis of Type 2 diabetes, while Chapter 3 assesses the rationale and possibilities for implementing screening of Type 2 diabetes in Denmark.

2.1 Diagnostic criteria for diabetes and impaired glucose tolerance

In 1999, a WHO Consultation Group published its recommendations regarding the diagnosis and classification of diabetes (6). The WHO recommendations have subsequently been followed by a number of countries. In Denmark, the scientific societies that have direct dealings with the diagnosis and treatment of Type 2 diabetes recommend that the WHO recommendations be followed.

The diagnosis diabetes is based on measurement of the concentration of glucose in the blood, possibly in combination with the presence of symptoms indicating that the patient has diabetes. In most cases, the diagnosis diabetes is made by measurement of the blood glucose level in the fasting state. Suspected diabetes can also be disproved in the same way. In cases where the diagnosis is uncertain, a tolerance test can be performed (oral glucose tolerance test, OGTT). The diagnosis diabetes mellitus can also be made in cases where the patient presents with clear diabetes-related symptoms (these are defined as thirst, excessive urination and weight loss) and with a blood glucose concentration exceeding 11 mmol/l.

Both the fasting glucose concentration and the concentration measured after an OGTT exhibit a certain degree of day-to-day variation (intraindividual variation) in the range approx. 7-15% (7, 8). Due to this day-to-day variation, the WHO recommends that at least two abnormal measurements taken on two different days should be available before the diagnosis can be considered certain (see below) (6).

The glucose content of the blood can be measured using several methods (see Section 2.2). The diagnostic criteria for diabetes based on measurements of the glucose concentration in blood and plasma (see below) are summarised in Table 2.1.1.
### TABLE 2.1.1
Diagnostic criteria for diabetes based on measurement of glucose in the fasting state and 2 hours after intake of 75 g glucose in 250 ml water (oral glucose tolerance test, OGTT)

<table>
<thead>
<tr>
<th>Glucose concentration [mmol/l]</th>
<th>Whole blood</th>
<th>Plasma</th>
<th>Venous</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Venous</td>
<td>Capillary</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting or 2-hour value</td>
<td>≥6.1</td>
<td>≥6.1</td>
<td>≥7.0</td>
</tr>
<tr>
<td><strong>Impaired glucose tolerance (IGT)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting and 2-hour value</td>
<td>&lt;6.1</td>
<td>&lt;6.1</td>
<td>&lt;7.0</td>
</tr>
<tr>
<td><strong>Impaired fasting glycaemia (IFG)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting and measured 2-hour value</td>
<td>5.6-6.0</td>
<td>5.6-6.0</td>
<td>6.1-6.9</td>
</tr>
</tbody>
</table>

The diagnosis diabetes mellitus is made in a person devoid of symptoms by measuring two diabetic values on different days. Impaired glucose tolerance (IGT) is a state in which fasting blood glucose is normal, whereas the measurement two hours after a glucose load is elevated (the border zone between normal and diabetic values). IGT is associated with an enhanced risk of developing diabetes and for the development of cardiovascular disease. Impaired fasting glycaemia (IFG) is a state in which the fasting value is close to the diabetic value. The prognostic value of IFG is unclear. In Denmark IFG is not used as a diagnostic unit, but persons with IFG should be investigated for diabetes by means of a glucose tolerance test.

### 2.2 Diagnosis based on various sampling methods

The diagnostic values for diabetes and reduced glucose tolerance (IGT) have remained largely unchanged since 1980 and have been reiterated in the WHO’s 1980, 1985 and 1999 reports on the diagnosis of diabetes. In 1999, the diagnostic value for fasting glucose was lowered, and the impaired fasting glycaemia (IFG) was concomitantly added as a new unit. As is apparent from Table 2.1.1, the diagnostic limits vary among the three different measurement methods based on the measurement of plasma or whole blood. This difference is primarily attributable to the fact that glucose is an energy source for the body cells, and that the concentration of glucose therefore decreases as it passes through the blood vessels. The other difference is between whole blood and plasma. Whole blood is a mixture of blood corpuscles and plasma, whereas plasma only consists of the aqueous components of the blood. As the glucose concentration is lower inside than outside the cells, the limit values are also correspondingly lower in whole blood. As is apparent from the above, the diagnosis can be based on venous plasma and on venous and capillary whole blood.

**Plasma** is the aqueous part of a blood sample. The plasma is retrieved by centrifuging the blood sample leaving the plasma as the upper layer in the vial. When this plasma has been pipetted off, the glucose content will remain stable, whereafter the sample can be sent to a laboratory. As the sample is stable, this sampling method is ideal for diagnostic use. The sample has to be centrifuged and the plasma pipetted off within 10 min of collection, however. Alternatively, the sample has to be placed in an ice bath, in which case it has to be centrifuged and the plasma pipetted off within 60 min. This can render the use of this method difficult in general practice as not all practices have a centrifuge and as the sample has to be processed immediately after sample collection.

**Capillary whole blood** is measured on a blood sample from the ear or finger. The sample is analysed immediately using a near-patient glycometer and thus does not need to be sent to a central laboratory. The major limitation is the lack of precision of the glycometer used. Only very few of the existing instruments yield a coefficient of variation that is low enough for the values to be suitable for diagnosing diabetes. At the same time, the instruments often have considerable bias, i.e. the instruments systematically measure too high or too low values. The use of near-patient glycometers for the measurement of capillary whole blood for diagnostic purposes thus requires that the instruments are documented to have a low coefficient of variation and that regular, systematic quality assurance of the glycometer is carried out to prevent systematic errors (bias).

**Venous whole blood** is measured on an ordinary venous blood sample, typically taken from the arm. As glucose is the main energy source for blood corpuscles, the glucose concentration decreases by approx. 0.5 mmol/hr following sample collection. A decrease of this magnitude can be of decisive significance if the
correct diagnosis is to be made. If the measurement of glucose is based on venous whole blood, the sample must be analysed immediately (within 10 min) or immediately cooled in an ice bath where it must remain until analysis is carried out, which should be no later than 60 min after sample collection. As measurement of venous whole blood entails more sources of error than the other two methods without the method affording other significant benefits, its use for diagnostic purposes cannot be recommended.

2.3 Prognosis in relation to diagnostic tests

According to the WHO recommendations, the diagnosis diabetes can be made in both the fasting state and through a glucose tolerance test. The American Diabetes Association recommends that the diagnosis be made on the basis of measurements in the fasting state, and that the diagnosis should only be made on the basis of measurements of plasma glucose (9). The reason why the WHO maintains that the diagnosis can be based on measurements of both fasting blood glucose and following a glucose tolerance test is the results of several pilot studies (cohort studies) in which groups of persons without previously detected diabetes and with a diagnosis made in connection with population-based screening have been followed for many years. The largest of these studies (DECODE study) encompassed almost 50,000 individuals, men and women of all ages, with a combined observation period exceeding 150,000 person-years. The study showed that every third person with diabetes is overlooked if the diagnosis is based solely on fasting glucose measurements (10) (1b). These European observations have subsequently been confirmed in population studies, among other places from Asia (11) (1b) (DECOD-Asia).

The DECODE study has also shown that the group with undetected diabetes (persons with high blood glucose after an OGTT) suffer a higher mortality and have a higher risk of developing cardiovascular disease than those who are identified solely on the basis of fasting blood glucose (12) (2b). On this background, the WHO recommends that an OGTT be carried out for diagnostic purposes if the fasting blood glucose value is in the high end of the normal range (corresponding to Impaired Fasting Glucose).

2.4 Organisation of diagnosis (general practice, central laboratories, etc.)

Each year 10,000-20,000 Danes develop diabetes, and as stated, approx. 100,000-150,000 are estimated to have diabetes without being aware of it. To identify these individuals a far larger group will have to be screened for diabetes, and ideally it should therefore be possible to make the diagnosis reliably, rapidly and at the lowest cost in terms of time and money for both the patient and the health service. At the same time diabetes is a serious diagnosis associated with considerable risk for the development of complications in the heart, circulation, eyes, kidneys and nerves that often requires extensive treatment (prophylactic pharmacotherapy and lifestyle changes). Finally, the diagnosis entails social consequences in the form of occupational limitations and changed insurance conditions. When the diagnosis is made, it therefore has to be reliable with the minimum risk of making a false positive diagnosis (the diagnosis diabetes in a person that does not have the disease). The benefits of rapid and simple diagnostic procedures therefore have to be weighed up against the risk of a false positive diagnosis.

The rapid and cheap diagnostic test is best carried out by the general practitioner through the use of a glycometer available in general practice (called a near-patient glycometer), while the most reliable measurement takes place at a central laboratory through the measurement of plasma glucose. In recent years, three studies (two Danish and one Finish-Danish) have analysed whether these methods can be used interchangeably in a diagnostic context by examining the relationship between plasma glucose (measured at the laboratory) and capillary whole blood (measured at the laboratory using an autoanalyser) (13) (1b), using near-patient glycometers (14) (1b), or a combination of several methods (15) (1b).

The first study, by Stahl et al., is a population-based study of 400 healthy persons without diabetes and without risk factors for the development of diabetes in which an OGTT was performed (13). The fasting plasma glucose values were significantly (0.5 mmol/l) higher than the corresponding values measured on capillary whole blood.

The second study encompassed 1,028 persons aged 40-69 years associated to three general practitioners in Aarhus (14). All patients in the relevant age group were invited to participate, and half accepted. The participants underwent a stepwise diagnostic programme with measurement of plasma glucose and capillary whole
blood glucose (Hemocue®) (determined in duplicate). The fasting values were 0.9 mmol higher in plasma than in whole blood, while there was no difference in the two-hour values.

The third study is a Finish-Danish study (15) encompassing individuals at high risk of developing diabetes recruited via advertisements in newspapers and other media. The glucose measurements (plasma and Hemocue) were carried out at several laboratories, and the study confirmed a difference of 0.9 mmol/l. In addition, the study showed that the measurement error of other near-patient glycometers was considerably higher, thus rendering them less suitable for diagnostic use.

Together the studies thus showed that the same degree of measurement certainty can be obtained with near-patient glycometers as with measurement of plasma glucose made at a central laboratory if the measurements made using near-patient glycometers are performed in duplicate. In addition, the study by Stahl et al. showed that systematic errors can easily arise in the form of deviations from the true value (bias) when using near-patient glycometers. This problem can be overcome by careful calibration and quality assurance of the glycometers used.

As regards weighing up between diagnostic simplicity and measurement certainty it can be concluded that plasma glucose (taken correctly) is the most precise measurement of the glucose level and should therefore be used wherever possible and appropriate. In general practice plasma glucose can be measured by the physician collecting the blood sample, centrifuging it, pipetting off the plasma and sending it to a central laboratory, as recommended by the Danish College of General Practitioners (16). Capillary whole blood can also be used for diagnostic purposes, but values in the grey zone should be confirmed by measurement of plasma glucose.

Irrespective of which measurement method is used, regular quality assurance of the method must be carried out. In practice, this is done for plasma glucose through national standardisation and testing through control samples. Corresponding quality assurance programmes for near-patient glycometers used in general practice have been established by some Counties, and is a precondition if such glycometers are to be used for diagnostic purposes.

Irrespective of which measurement method and type of blood sample are used, the glucose level will vary from day to day due to biological variation. This applies in both the fasting state and following a glucose load, where the biological day-to-day variation (which is not due to uncertainty in the measurement method) is 3-5%.

In order to ensure that the diagnosis diabetes is not made erroneously, the diagnosis must be confirmed by repeated measurement of blood/plasma glucose on another day unless the person has classical, clear symptoms of diabetes, cf. the WHO recommendations (6).

**Subconclusion**
- The diagnosis diabetes can be made in the fasting state and after an oral glucose tolerance test (OGTT)
- Measurement of plasma glucose is more precise than measurement of blood glucose (1b)
- A glucose tolerance test should be carried out on persons having a fasting plasma glucose level in the upper normal range since a diabetic state can otherwise be overlooked (as recommended by the WHO) (1a)
- Near-patient glycometers for measurement of blood glucose at the general practitioner require continued calibration and quality assurance (1b).

2.5 Health economic assessment of various diagnostic strategies

This section concerns the socio-economic consequences of selecting various diagnostic strategies. An assessment is made of the direct costs to the health service and the indirect costs of each of the following three diagnostic strategies:

Model 1: Sample collection and analysis of whole blood glucose in general practice.
Model 2: Sample collection in general practice and analysis of plasma glucose at central laboratories
Model 3: Sample collection and analysis of plasma glucose at central laboratories.

The three diagnostic strategies are described in Annex 3. The calculations assume that the patient has already been assessed as being at high risk of having diabetes, and hence do not include the consultation during
which the patient is detected as being at high risk. The figures provide qualified estimates of the percentage of high-risk patients that will have to undergo the individual elements of the screening strategies. The basis upon which these qualified estimates have been made is described in Annex 3.

2.5.1 Data and methods

The costs of control and treatment are calculated as the total direct treatment-related costs, i.e. costs are included irrespective of who pays. The indirect costs in the form of time consumption by the patients and their lost earnings are calculated separately. The correct valuation of time consumption by the patients is a controversial issue. Based on the production value approach\(^1\) the loss of production during short-lasting absence to attend a physician may well be negligible because the work is undertaken on other occasions. Despite this uncertainty, a sensitivity analysis has been carried out yielding figures corresponding to 0-100% of the average wage. The unit costs are based on the National Health Insurance fees (17), a private laboratory’s fees (18) and the hourly wage figures from Statistics Denmark (19), as documented in Annex 4\(^2\). The costs of carrying out a glucose tolerance test (OGTT) should reflect the extra consumption of resources entailed by the procedure. The practice in this area varies from one part of Denmark to another. In Aarhus County, the cost of an extra consultation can be added in that it has been determined that this is in good accordance with the extra consumption of resources (20). This is not included in the normal interpretation of the National Health Insurance fees (21). In the present report we use the normal interpretation of the National Health Insurance fees. A sensitivity analysis has therefore been carried out, revealing that the results are largely independent of which method is used to set the cost of carrying out an OGTT, cf. the note in Table 2.5.2.1.

2.5.2 Results

The cost calculations for the three diagnostic models are shown in Table 2.5.2.1 (direct costs to the health service) and Table 2.5.2.2 (indirect costs).

**TABLE 2.5.2.1**

<table>
<thead>
<tr>
<th>Costs per diagnostic examination</th>
<th>[DKK]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1: Diagnosis in general practice</td>
<td>160</td>
</tr>
<tr>
<td>Model 2: Combined diagnosis</td>
<td>270</td>
</tr>
<tr>
<td>Model 3: Diagnosis at laboratories</td>
<td>90</td>
</tr>
</tbody>
</table>

If the cost of a glucose tolerance test is assumed to entail two consultation fees instead of one, the costs for Model 1 and 2 both increase by DKK 10 per diagnostic examination.

**TABLE 2.5.2.2**

<table>
<thead>
<tr>
<th>Cost of time consumed by patients per diagnostic examination</th>
<th>[DKK]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1: Diagnosis in general practice</td>
<td>0-150</td>
</tr>
<tr>
<td>Model 2: Combined diagnosis</td>
<td>0-160</td>
</tr>
<tr>
<td>Model 3: Diagnosis at laboratories</td>
<td>0-480</td>
</tr>
</tbody>
</table>

Travelling time to the general practitioner is assumed to be 2x10 min, and to the laboratory 2x30 min. The estimates are sensitive to changes in these assumptions.

Measured solely against the direct costs to the health service, diagnosis at central laboratories (Model 3) is the most advantageous in that diagnosis carried out partly or completely in general practice is considerably more expensive than diagnosis carried out at laboratories (Table 2.5.2.1).

If one from the socio-economic viewpoint includes the cost of time consumption by the patients in the total costs, and if one is concomitantly willing to set the value of this to the average hourly wage (column 2, Table 2.5.2.2), then the picture changes and Model 3 becomes the most expensive means of carrying out diagnosis. Including the cost of time consumption by the patients, the total costs are thus DKK 570 per diagnostic examination for Model 3 as compared with DKK 310 per diagnostic examination for Model 1 and DKK

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1. i.e. that the value of lost working time is calculated as the value of the production that is lost due to the fact that a person is absent from work.
2. The fees are not necessarily equivalent to the actual costs. The laboratory fees are based on detailed cost calculations. No cost studies are available in the National Health Insurance area indicating to what extent the negotiated fees might deviate from the actual costs. Moreover, the National Health Insurance fees and laboratory fees have the advantage that they reflect the true costs that the public sector may pay in the case of changes in activity.

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430 per diagnostic examination for Model 2. From the overall economic point of view Model 1 is cheaper than Model 3 provided one is willing to set the value of time consumption by the patients to more than 20% of the average hourly wage, while Model 2 is cheaper than Model 3 provided one is willing to set the value of time consumption by the patients to more than 54% of the average hourly wage.

Comparison of the two models in which diagnosis is performed partly or completely in general practice reveals that from a narrow economic point of view Model 2 is inferior to Model 1 in that the latter is more expensive than Model 1 for all time values.

Looking narrowly at the Danish economy, Model 1 must therefore be considered to be the best.

Models 2 and 3 have potential non-economic advantages, however, among other things in relation to quality assurance. Moreover, relative to the treatment costs of just under DKK 5,000 annually (cf. Section 5.4.2), the costs of diagnosis are rather insignificant.

The number of diagnostic examinations initiated in Denmark is unknown, but if the number of new cases of diabetes is 10,000-20,000/yr, cf. Section 2.4, and it is assumed that 3-5 diagnostic examinations are initiated for each newly diagnosed case3, between 30,000 and 100,000 diagnostic examinations will be performed each year, corresponding to DKK 3-27 million annually in direct costs to the health service, which is relatively modest relative to the annual costs of regular control and drug treatment of Type 2 diabetes patients (approx. DKK 575 million).

**Subconclusion**

- Focusing solely on the direct costs, diagnosis is cheapest at the laboratories.
- If the indirect costs are included (e.g. the screened person’s lost wages), and if time consumption is valued at more than 20% of the average hourly wage, diagnosis is cheapest in general practice (Model 1). These calculations are sensitive to estimates of the patient’s time consumption, however.
- The annual costs for diagnosis are estimated at DKK 3-27 million.

### 2.6 Conclusions and recommendations

**Conclusions**

- The diagnosis diabetes can be made in the fasting state and after an oral glucose tolerance test (OGTT).
- Measurement of plasma glucose is more precise than measurement of blood glucose (1b).
- The diagnosis diabetes must – in patients without symptoms – be based on at least two independent measurements of glucose performed on different days which both show diabetic values. This is necessary in order to minimise the risk of incorrectly diagnosing a person without diabetes as having the disease.
- A glucose tolerance test should be carried out on persons having a fasting plasma glucose level in the upper normal range since a diabetic state can otherwise be overlooked (as recommended by the WHO) (1a).
- Apparatus and procedures relating to near-patient glycometers for measurement of blood glucose at the general practitioner require, like at the hospital, continued calibration and quality assurance (1b).
- The new category defined by the WHO and the American Diabetes Association – Impaired Fasting Glycaemia – has no documented place in routine clinical work (but could be a relevant object for continued research) (1a).
- Focusing solely on the direct costs, diagnosis is cheapest at laboratories.
- If the indirect costs are included (e.g. the screened person’s lost wages), and if time consumption is valued at more than 20% of the average hourly wage, diagnosis is cheapest in general practice (Model 1). These calculations are sensitive to estimates of the patient’s time consumption, however.
- The direct costs for diagnosis are of the order DKK 3-27 million annually, which is relatively modest relative to the annual costs for regular control and drug treatment.

**Recommendations**

- It is recommended that the WHO diagnostic criteria should be adopted, including the recommendation that in the case of symptom-free patients the diagnosis should be confirmed through repeated measurement of glucose on another day (B).

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3 The number of diagnostic examinations per case will depend on how the persons are selected for diagnostic examination, i.e. whether they are detected via case finding, population screening or a high-risk screening strategy.
Introduction of the new category “Impaired Fasting Glycaemia” in Danish diagnosis and disease classification cannot be recommended at present (A).

The diagnosis diabetes can be made at central laboratories or with near-patient glycometers (in both cases with quality-assured procedures and methods) (A).

Apparatus and procedures that are used for diagnostic purposes must be regularly quality-assured through national or regional quality assurance programmes. This applies to apparatus and procedures used at both central laboratories and in general practice (B).

Diagnosis of diabetes shall be based on the measurement of plasma glucose carried out in accordance with the sample handling recommendations (immediate centrifugation and pipetting off or immediate cooling in an ice bath and centrifugation or measurement within 60 minutes) (A). The analytical quality requirements for measurement of plasma glucose are: bias $<0.1$ mmol/l; imprecision $\leq 2.5\%$.

Alternatively, diagnosis can be based on capillary whole blood analysed on quality-assured near-patient glycometers and with a measurement uncertainty of the same order as with the analysis of plasma samples. Due to the greater measurement uncertainty, double determination should be carried out, i.e. determination of the same blood sample on two occasions (A). For measurement of capillary whole blood the analytical quality requirements are: bias $<0.2$ mmol/l; imprecision $\leq 4\%$, corresponding to 0.2 mmol/l in the diagnostic area for fasting blood glucose measurements.

Capillary whole blood measurements in the interval 6.1-7.5 mmol/l must be confirmed through measurements based on plasma glucose.

With glucose measurements close to the diagnostic area (fasting plasma glucose 6.1-6.9 mmol/l or capillary whole blood glucose 5.5-6.0 mmol/l), the patient must be offered further examination with a glucose tolerance test and risk factor assessment for cardiovascular disease (B).
3 Screening for Type 2 diabetes

Surveys based on patients with newly detected diabetes diagnosed either in general practice or in the hospital service have shown that 30 to 50% of all newly diagnosed Type 2 diabetes patients have one or several signs of complications at the time of diagnosis (22, 23), thus reflecting that they have had the disease for many years prior to being diagnosed. It is on this background that the American Diabetes Association (ADA) in 1997 (9) recommended screening for Type 2 diabetes from the age of 45 (in contrast to previously when screening of high-risk groups was recommended). A Danish report from 2000 published in the journal of the Danish Medical Association recommended more active case finding among high-risk individuals (although without recommending screening for Type 2 diabetes).

Early case finding and screening for Type 2 diabetes can be established at several levels differing in intensity, as described in Figure 3.1.

**FIGURE 3.1. Screening, examination and diagnosis of Type 2 diabetes**

**Definitions used in Figure 3.1**

- **Step 1:** Describes the intensity with which the case finding or screening is to take place. It encompasses:
  - Clinical case finding: identification of cases among patients who exhibit actual signs of the disease.
  - Intensified case finding: opportunistic screening: more active identification among persons in high-risk groups.
  - Stepwise case finding: the risk scoring model: Stepwise screening model, where the first step is the use of a high-risk score to identify individuals at high risk.
  - Population screening: screening activity where the whole population (in specific age groups) is the target of the screening.

- **Step 2:** Investigation: Concerns the decision as to which individuals identified in connection with Step 1 will proceed to diagnostic examination.

- **Step 3:** Diagnosis: Concerns the choice of diagnostic strategy, including classification and analysis methods, as described in Chapter 2.

The decision as to whether to establish screening for a given disease has among other things to be based on the severity of the disease, the validity of the screening test, the treatment possibilities and the economy. In 1968, Wilson and Jungner, on behalf of the WHO, described 10 requirements that had to be met in order for screening to be considered relevant (24). These 10 requirements have subsequently been expanded to 14 as described in the National Board of Health report of 1990, “Screening – hvorfor – hvornår – hvordan?” (Screening – why – when – how?) (25).

1. The disease has to comprise a serious health problem
2. Acceptable and effective treatment has to be available for patients identified as having the disease
3. Diagnosis and treatment facilities have to be available
4. The disease has to be detectable in a latent or early symptomatic stage
5. Appropriate tests or examination methods have to be available
6. The test/examination method has to be acceptable to the population
7. The course of the disease if untreated has to be adequately elucidated – including the development from the latent to the manifest stage
8. The indications for treatment have to be clearly defined
9. The costs of case finding (including of diagnosis and treatment of patients) have to be reasonable relative to the health service’s total expenses
10. Screening efforts have to be a continuous process and not a one-off event
11. The validity, technical effectiveness and predictive value of the screening methods have to have been described
12. Ethical, psychological and psychosocial consequences of screening (incl. of false negative and false positive test results) have to have been described
13. The health economic consequences of screening have to have been described
14. Detailed descriptions of organisation, management, resources, education and patient information have to be available.

In the following these 14 points are systematically examined in five sections, each referring to one or several of the 14 requirements. The chapter concludes with an overall recommendation about screening.

3.1 Characteristics of Type 2 diabetes

**Requirement 1: The disease has to comprise a serious health problem:**
Diabetes is a major health problem due to its magnitude (200,000-300,000 persons with diabetes in Denmark), the character of the disease and the fact that at least 7% of the total health expenses are used on the treatment of diabetes and the associated complications (3, 5).

**Requirement 4 and 7: The disease has to be detectable in a latent stage, and if untreated the course of the disease from the latent to the manifest stage has to be adequately elucidated:**
Approximately half of all Type 2 diabetes patients aged 30-60 years do not know that they have the disease. Therefore these patients do not receive relevant treatment and do not undergo regular screening for complications. The course of the disease in the undiagnosed phase cannot be described precisely as the time of onset of the disease cannot be established. Surveys from the USA and England (22, 23) based on patients with newly diagnosed diabetes show, however, that 20 to 30% of the patients have diabetic retinopathy at the time of diagnosis, that an equivalent proportion have signs of diabetic nephropathy, while the proportion of persons with signs of cardiovascular disease varies (due to differences in the definition of cardiovascular disease and in the composition of the patient population). Overall, approx. 50% of all patients with newly diagnosed Type 2 diabetes have one or more complications at the time of diagnosis. The probable latency from the onset of the disease to clinical diagnosis is estimated at between 5 and 11 years (26) (4).

**Subconclusion**
- Type 2 diabetes comprises a major health problem (1a)
- Type 2 diabetes can be demonstrated in a latent stage 5-11 years before the disease would otherwise be diagnosed (when the disease causes symptoms) (1b)
- This latent diabetes is believed to have already led to complications at the time of diagnosis in up to 50% of the patients. These complications can potentially be prevented by early treatment (1c).

3.2 Evaluation of diagnostic tests and screening strategies

**Requirement 5, 6, and 11: Appropriate tests or examination methods have to be available, they have to be acceptable to the population, and their validity, technical effectiveness and predictive value have to have been described:**
The purpose of undertaking screening for Type 2 diabetes is to identify persons with diabetes without or with only very discrete clinical symptoms of diabetes.

When evaluating the **validity of the test system** the screened population is divided into the following categories: True positives, who are the persons who directly benefit from the screening as they will be diagnosed earlier than with clinical case finding. True negatives, who are the persons who are comforted on a true foundation. False negatives, who are the persons who have the disease, but who are found to be healthy during screening and who are given a false security, which in the last analysis can lead to delayed diagnosis. False positives, who test positive on screening, but who are in reality healthy. These are subjected to further diagnostic investigation and possibly made to worry unnecessarily. The psychological consequences of being labelled as false positive and false negative are examined in Section 3.4.
### 3.2.1 Concepts

**TABLE 3.2.1**

Possible outcomes of a screening test. The person identified as being ill by the test can actually be ill or healthy, and the person identified as being healthy can actually be healthy or ill.

<table>
<thead>
<tr>
<th>Test</th>
<th>Diagnosis</th>
<th>Ill</th>
<th>Healthy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ill</td>
<td></td>
<td>( a ), true positive</td>
<td>( b ), false positive</td>
</tr>
<tr>
<td>Healthy</td>
<td></td>
<td>( c ), false negative</td>
<td>( d ), true negative</td>
</tr>
</tbody>
</table>

| Sensitivity: \( \frac{a}{a+c} \) | Specificity: \( \frac{d}{b+d} \) |

Table 3.2.1 depicts the possible categorisation of a person by a screening test.

The **sensitivity** is the probability of being tested positive given one is ill, i.e. the proportion of the ill persons detected by a given test. The **specificity** is the probability of being tested negative given one is healthy. Sensitivity and specificity are measures used to assess the validity of screening tests. They are measures of how well the individual test discriminates between ill and healthy persons. They are therefore important measures for the health authorities when having to decide on implementation of a given test. The number of both false positive and false negative should be minimised. With a high sensitivity there will be few false negative answers, and with a high specificity there will be few false positive answers. The sensitivity increases at the expense of specificity. The attainment of a higher sensitivity will entail that more healthy persons test positive, resulting in a fall in specificity. The optimal will be a test with as high sensitivity and specificity as possible.

**True positive rate (positive predictive value (PPV)):** is the probability that a person is ill given a positive test result, i.e. how certain is it that the person is ill when the test is positive? **True negative rate (negative predictive value (NPV)):** is the probability that a person is healthy given a negative test result, i.e. how certain is it that the patient is healthy when the test result is negative? The predictive values are very important measures for both physician and patient. When the positive predictive value is low the test results should be interpreted with caution, i.e. one has to inform the patient that even though the test result is positive, it is not certain that the patient is ill. Conversely, a high negative predictive value can be used to assure the patient and physician that the patient is healthy.

The predictive values are dependant on the prevalence of the disease in the individual population groups. In populations with a high disease prevalence the predictive values for a test will always be higher than in populations with a lower disease prevalence.

In addition to the above, screening tests also need to be simple, near-patient (it would be an advantage if they can be used in general practice), cost-effective, safe and acceptable to both the health service and the population in general.

### 3.2.2 Suitable tests or examination methods

**Requirements to screening tests versus diagnostic tests for diabetes**

**Screening test:** The ideal screening test has to be simple, possible to carry out anytime during the day, not time-consuming and possible to use near-patient, preferably at or in connection with general practice. It should have high sensitivity, which typically leads to loss of specificity. None of the presently used screening tests for diabetes meet all these requirements.

**Diagnostic test:** The ideal diagnostic test has to be safe with high specificity. As it is typically undertaken as step 2 in a diagnostic examination of a considerably smaller proportion of the population and on individuals with a high disease risk, a test entailing higher costs and more inconvenience to the patient and physician is typically accepted.

The purpose of the screening test is thus to identify individuals with a high risk of having the disease, while the diagnostic test is the final confirmation of whether or not the individual has a given disease. Usually there is a clear difference between a screening test and a diagnostic test. Classical examples are screening for cervical cancer and for breast cancer where vaginal smear and mammography, respectively, are used as screening tests, while the diagnosis is made on the basis of a tissue sample. With diabetes there is no such clear distinction as measurement of blood or plasma glucose is often part of screening tests. Screening tests and diagnostic
tests (fasting plasma glucose or oral glucose tolerance test) thus become identical, thereby making calculation of sensitivity and specificity impossible.

The following possibilities for screening for Type 2 diabetes are examined below:

- The use of questionnaires/risk scoring systems
- Measurement of HbA1c/glycosylated haemoglobin, which is an expression of the average glucose level over the past approx. 2-3 months)
- Measurement of random blood glucose (RBG)
- Measurement of fasting blood glucose (FBG)
- Combined strategies.

The applicability of the oral glucose tolerance test (OGTT) as a screening test is not examined as the test is developed and established as a diagnostic tool and not as a screening instrument. At the same time the test is troublesome and costly and requires that the test person is in a fasting state. The WHO thus also recommends that measurement of fasting plasma glucose is used as the primary test, and that persons with plasma glucose high in the normal range (IFG) subsequently undergo an OGTT. Likewise the possibility for using fructosamine is not examined as the method is very rarely used in Denmark.

The different screening strategies are summarised in Table 3.2.2. Examination of the possible use of urine test strips for screening has not been included in this HTA report as it is regarded as an obsolete analysis in this connection.

**Questionnaires**

During the last eight years, several different risk scoring systems have been developed in the form of simple questionnaires and score systems based on information that is usually available in the records kept by the person’s general practitioner. The advantages of the risk scoring systems are that they are non-invasive, the price is reasonably low, and the systems can be undertaken anywhere and anytime. Questionnaires can be used in population screening programmes or as part of a systematised case finding via general practice.

The individual risk scoring systems contain different degrees of information about symptoms of and risk factors for diabetes. These pieces of information are simple and easy to use in a simple questionnaire (27-29) (1b). A few of the models contain information that can be retrieved via the general practitioner’s patient record system (30) (2b) (31) (1b).

The more pieces of information (parameters) included in the individual risk scores, the greater the sensitivity obtained. By including many pieces of information the models often become more complicated. This can lead to them becoming less acceptable for the population, and as a possible consequence of this, more people might not want to take part in a screening programme.

The scoring systems have all been developed on the basis of cross-section studies. In the studies (27-29, 31) (1b) the scoring systems are further tested on a different cohort than the one on which they were developed. The sensitivity of the different scoring systems is relatively high, 75-80%, whereas the specificity fluctuates between 35 and 56%. A single study by Griffin et al. (30) (2b) has not tested the risk scoring on an independent population group, but has divided data from the population group into two halves. One half has been used for developing the score, the other half for validation. Sensitivity and specificity of this score are 77% and 72%, respectively. None of these tools are optimal, but can be used for identification of high-risk individuals in a stepwise screening strategy where a questionnaire would be the first step.

**For which age groups is it reasonable to use risk scoring systems?**

Age is included in several scoring systems as the most important risk factor and therefore contributes with many points to the total risk score. In a Danish questionnaire (not yet published) the age 60 years gives a score of 4 points (in comparison, familial disposition in two or more of the closest family or BMI above 30 gives a score of 2 points) as more than one in ten 60-year-old Danes has diabetes. Correspondingly, the prevalence of diabetes in very young persons is very low. The application of a score system among young people (0-35) entails a high proportion of false positive answers. The risk scoring systems are therefore most suitable for the age group 35-55 (possibly 60) years. With the age group under 35 years, the efforts should be directed at the detection of persons with clinical symptoms (clinical case finding) and intensified case finding among people with very high risk (women with gestational diabetes, persons with massive familial
disposition, and immigrants of Asian origin). Among persons over 60 years old the prevalence of unrecognised diabetes is so high (6-10%) that the existing risk scoring systems are not suitable. Here there is a need for the development of more sensitive instruments for risk assessment.

**Glycosylated haemoglobin**

Glycosylated haemoglobin (HbA1c) can be measured on both venous whole blood (blood sample from the arm) and capillary whole blood (blood sample from the ear lobe). The advantages of measuring glycosylated haemoglobin are that the method does not require any preparations of the patient and can be taken at any time.

Glycosylated haemoglobin exists in a number of different forms. The most frequently used and most stable measurement is of HbA1c. HbA1c is a good measure of a possible permanent elevation of the blood glucose concentration as it reflects the average blood glucose during the preceding 2-3 months. Moreover, measurement of HbA1c is often used to assess glycaemic regulation in patients with Type 2 diabetes. For many years it has been a matter of discussion whether HbA1c can be used for the diagnosis of diabetes. This is problematic. Davidson et al. (32) have shown that 60% of persons diagnosed on the basis of fasting plasma glucose of between 7.0 and 7.7 have got a normal HbA1c.

The question is: Can HbA1c be used as a screening tool? And if affirmative: What limitations apply to HbA1c?

Many of the existing studies concerning assessment of HbA1c as a screening tool have chosen a high cut-off value for HbA1c, which is not relevant in a screening context as according to the findings of Davidson, this will entail many false negative results. Studies with cut-off values from 5.8 to 6.3% have found a sensitivity of 66-95% and a specificity of 67-98% (see Table 3.2.2).

There are great differences between the individual studies. Among other things, this is due to great differences as to which persons are included in the individual studies. In some studies, patients with Type 2 diabetes are included, while other studies are based on blood samples from persons with a high risk of developing the disease.

A substantial limitation in the use of HbA1c is the great difference between the various HbA1c analyses on the market. It is therefore difficult to compare HbA1c values measured at different laboratories. In the past neither national nor international standards existed for HbA1c analyses, which made the establishment of screening cut-off values difficult. In 2002, an international standard for the HbA1c analysis was developed, but until this is fully implemented it is not possible to use HbA1c as a screening tool. The standardisation of the HbA1c analysis, however, will not mean that HbA1c measurements can be directly used as a screening instrument as the relationship between HbA1c and the glucose concentration is relatively poor in the normal and low range (grey zone between “normal” and “diabetic”).

**Random blood glucose**

A blood glucose measurement made at a random time of the day is called a random blood glucose. No account is taken of when the patient has eaten. The advantage of the random blood glucose is that the person does not need to be fasting, and that the sample can be analysed using a near-patient glycometer, and hence one gets an answer immediately after the sampling. The applicability of random blood glucose as a screening instrument is assessed in a few studies (33) (4) (34) (4). The problem with these studies is that they use serum glucose or capillary glucose as the reference method, and these are not optimal. They also use high cut-off values, which results in low sensitivity. Engelgau (33) (4) finds that there is a relationship between age and random blood glucose, and suggests age-specific cut-off values. At the same time, both Engelgau and Simmons (34) (4) find, not surprisingly, that the time interval between having eaten and being tested is of importance for the sensitivity and the specificity. If these factors are to be taken into consideration, measurement and interpretation of random blood glucose becomes complicated. Random blood glucose can be used to exclude diabetes, however, in that a random plasma glucose <5.5 mmol/l or a random capillary blood glucose <4.5 mmol/l signifies that diabetes is unlikely.

**Fasting blood glucose**

Fasting blood glucose has to be taken after eight hours of fasting, which means that the person is not allowed to eat or drink for eight hours before collection of the blood sample. Glucose can, as described in Chapter 2, be measured on plasma, capillary whole blood and venous whole blood.
If fasting glucose is to be used as a screening test, it is vital that cut-off values are used that are lower than the diagnostic cut-off of 7.0 mmol/l. The reason for this is among other things that the DECODE study, a European multicentre study with the participation of 13 centres distributed all over Europe, has shown that if a fasting glucose of 7.0 mmol/l is used as the diagnostic cut-off, 1/3 of the persons with diabetes will be misclassified as healthy as only their 2-hour value is diabetic. This is the rationale behind the WHO recommendations that persons with a fasting glucose high within the normal range have to undergo an OGTT. It is therefore vital that the cut-off values for fasting glucose used in screening are lower than the diagnostic limit. When reviewing the literature, cut-off values lower than 7.0 mmol/l have therefore been assessed. Big differences are found between the individual studies. This might partly be due to population differences (e.g. in some studies the test has only been applied to persons with a particularly high risk of developing diabetes), partly to methodological differences in the glucose measurements. Some studies have further included persons with known Type 2 diabetes in the analyses, and as these persons typically have considerably higher fasting glucose values, the sensitivity of the method is artificially increased. Cut-off values for fasting plasma glucose of 5.7-6.5 yield a sensitivity and specificity of 68-88% and 76-97%, respectively. When measuring fasting capillary glucose the same results are obtained.

**Combined strategies**

As is apparent from the above section, all the strategies based on simple methods are subject to considerable problems. If the screening cut-off point is set too low (with respect to risk score, blood glucose or HbA1c), many persons will have to proceed to diagnostic examination, and of these only few will have the disease. The proportion of false positive will therefore be high. This increases pressure on individuals and the health service. If the cut-off point is set too high, few will have to proceed to diagnostic examination, but many persons with diabetes will wrongly be characterised as healthy (false negatives).

These problems can be reduced by combining several strategies where two or more of the following parameters – questionnaires, HbA1c, random blood glucose or fasting glucose – are combined. Two studies have compared combinations of HbA1c and fasting plasma glucose (35) (2b) and fasting plasma glucose and HbA1c or glycosylated fructosamine (36) (2b). By using these combined strategies higher positive predictive values are obtained. The above-mentioned combination models require considerable further development and validation before they can be implemented in daily clinical practice, however.

**Subconclusion**

- Validated screening tests are available where the validity, sensitivity, specificity and predictive value are known. Most tests only entail minimal physical discomfort and should therefore be acceptable (2b).
- At present there are no studies that have systematically assessed a screening strategy based on case finding of individuals with a high risk of developing diabetes using questionnaires and subsequent analysis of non-fasting blood samples, which will minimise the number of fasting blood samples and the number of glucose tolerance tests. Neither is there literature that has assessed the population's reaction to these screening strategies. Such a study is ongoing in Denmark (37) – the results are expected during the course of 2004.
- Finally, there are no simple screening methods with high sensitivity (>90%) that concomitantly have an acceptable, high specificity (>80%). For this reason it will not be possible to carry out simple, reliable screening for diabetes (2a).
- If more intensive case finding of persons with undetected diabetes is to be carried out the recommendation at present is that the general practitioners should enhance the focus on persons who are overweight and physically inactive, as well as on women with gestational diabetes and persons with familial accumulation of diabetes (5).
### Overview of the various screening tests for type 2 diabetes

<table>
<thead>
<tr>
<th>Method/test</th>
<th>Use/assumptions</th>
<th>Cut-off</th>
<th>Sensitivity/ Specificity (%)</th>
<th>Comments: Screening vs. diagnosis</th>
<th>Evidence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Questionnaires</td>
<td>Good in a stepwise screening strategy. Reduces the number of blood samples. Can be sent by post or handed out in general practice. Used for the age group 40-70 years.</td>
<td>Cut-off is specific for the individual questionnaire</td>
<td>Sens: 70-80 Spec: 35-56</td>
<td>Only screening</td>
<td>1b</td>
<td>(27-29, 3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2b</td>
<td>(30)</td>
</tr>
<tr>
<td>HbA1c (glycosylated haemoglobin)</td>
<td>The persons do not have to be fasting. Can be taken in general practice. Can be collected from the ear or finger. National standards need to be specified for the analysis methods.</td>
<td>5.8-6.3</td>
<td>Sens: 66-95 Spec: 67-98</td>
<td>Only screening Not diagnosis</td>
<td>2a</td>
<td>(38)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2b</td>
<td>(36, 39-41)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3b</td>
<td>(42)</td>
</tr>
<tr>
<td>Random blood glucose</td>
<td>The persons do not have to be fasting. Good in a stepwise screening strategy. Reduces the number of diagnostic tests. Can be collected from the ear or finger. Can be measured and analysed in general practice. Answer immediately available.</td>
<td>6.1-8.0</td>
<td>Sens: 34-90 Spec: 80-97</td>
<td>Only screening</td>
<td>3b</td>
<td>(43)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>(33, 34)</td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>The persons have to be fasting. Has to be taken in the morning. When measuring plasma glucose (FPG) the answer cannot be given immediately. When measuring blood glucose (FBG) the answer can be given immediately.</td>
<td>FPG: 5.7-6.5 Sens: 68-88 Spec: 76-97</td>
<td>When using fasting values, approx. 2/3 of the persons with Type 2 diabetes will be detected by the initial test</td>
<td>2b</td>
<td>(44-53)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FPG: 5.0-6.7 Sens: 75-83 Spec: 79-93</td>
<td></td>
<td></td>
<td>2b and 3b</td>
<td>(54)</td>
</tr>
</tbody>
</table>

#### 3.3 Is documentation available that screening affects the prognosis?

**Requirement 2: An acceptable and effective treatment has to be available for patients identified as having the disease:**

In Chapter 5 it is concluded that the medical (pharmacological and polypharmacological) treatment of Type 2 diabetes affects their morbidity in particular, and the reader is therefore referred to that chapter.

**Requirement 8: The indications for treatment have to be clearly defined:**

The question now is: Is there a clear treatment indication for patients with newly diagnosed diabetes? The question can be reformulated as: Is documentation available that screening and early intervention and treatment entail a better prognosis for the patient than that observed in patients diagnosed with clinical symptoms combined with subsequent optimal pharmacological and non-pharmacological (behavioural) treatment?

No good, prospective, randomised studies have hitherto been undertaken documenting an effect of screening and early intensive treatment on the prognosis. One Danish-led international study seeks to elucidate this issue, but the results cannot be expected until 2007-2008 (37). A few studies exist, though, which use modelling of data from epidemiological studies and results from intervention studies in an attempt to estimate the effect of screening and early intervention as compared with intensified case finding or systematic screening. These studies will be examined in Section 3.6.

**Subconclusion**

- There is evidence that through intensive treatment of blood glucose, blood pressure and blood lipids, both medical treatment and lifestyle changes can improve the prognosis in patients with diabetes diagnosed on the basis of clinical symptoms (1a).
- There is a need for good documentation showing that screening and subsequent early intensive treatment of patients detected by screening reduce the risk of developing complications and reduce mortality, although this can be assumed to be the case based on epidemiological studies.

#### 3.4 The patient perspective. Psychological and social consequences of screening for Type 2 diabetes

**Requirement 12: Ethical, psychological and psychosocial consequences of screening (incl. false negative and false positive test results) have to have been described:**

In a screening process an individual who perceives of himself as healthy, will be subjected to an investigation programme that typically encompasses a stepwise assessment such as illustrated in Figure 3.4.1. In all steps of the screening process the outcome can be “healthy or ill”, and each time the outcome can be correct (true) or incorrect (false).
FIGURE 3.4.1.

To be offered a screening examination can be presumed to entail psychological and/or social consequences, even in those situations where the person can rapidly be categorised as healthy. Factors such as waiting period for examination, further examinations, which authority undertakes the diagnostic examination, and the result of the investigation can also be presumed to affect the magnitude of the consequences.

This section reviews the existing knowledge about psychological and social consequences of screening for Type 2 diabetes, including the consequences of:

- Being invited for a screening examination
- The waiting period prior to the examination
- Being risk-assessed through a single screening test
- Initially getting a positive or “perhaps” positive answer, subsequently to be declared healthy
- Being declared ill.

Where relevant knowledge is available, moreover, suggestions for prevention of negative consequences will be given. Finally, the section will touch on the problems with non-responders, i.e. the group of persons who choose not to undergo screening despite being so advised. Psychological and social consequences of having diabetes are not included in this analysis as they do not have specific relevance for decisions on the possible implementation of screening for Type 2 diabetes.

A literature search has been conducted in the databases PubMed, Embase, CINAHL and PsykInfo within the disease categories diabetes, cardiovascular disease and cancer as only few studies were identified that elucidate the consequences of screening for Type 2 diabetes. Presumably, however, the existing knowledge about psychological and social consequences of screening for other chronic diseases and other risk factors (such as hypertension and hypercholesterolaemia) to a greater or lesser extent can be transferred to Type 2 diabetes. In the same way it was found appropriate to include knowledge and experience from screening investigations of more serious chronic diseases/malignant conditions. Documentation for psychological and social consequences of screening can thus be collected from three levels:

- Screening for Type 2 diabetes
- Screening for other chronic diseases and risk factors
- Screening for more serious chronic diseases/malignant conditions.

3.4.1 “Invitation” to screening for Type 2 diabetes

The offer to take part in a screening programme can have both benefits and drawbacks. The offer can be conceived of as a reassuring measure such that one feels sure that one is healthy. On the other hand, it has also been pointed out that the offer can cause a feeling of guilt whether the individual accepts the offer or not. The background for this reaction is that the screening programme has been initiated by health service experts and politicians, who thereby set norms for “the right” health behaviour. As a consequence, the persons
who do not follow the norms, including participation in a screening programme, might consider themselves “sinners”. A Danish study has examined the consequences of screening for diabetes with postally distributed urine test strips that the recipients should use themselves and subsequently submit the results for assessment (55). The study used interviews as the data source and showed among other things that the offer was conceived of in such a way that if one did not test oneself and react to the offer, it would be one’s own fault if the disease was there anyway and complications such as blindness arose because treatment was not instigated in time.

A few articles examined what information should be provided in invitations to screening in general (56). Suggestions for what information should be provided in connection with an invitation to screening for Type 2 diabetes are listed in Figure 3.4.2.

FIGURE 3.4.2. Information that should be provided in an invitation to screening for Type 2 diabetes (inspired by Marteau 1990 (56))

- The reason the patient in question has been called in (e.g. belongs to a specific age group or a specific physician)
- Description of the risk entailed by having Type 2 diabetes
- How participation in the screening programme can reduce this risk
- The test procedure
- How and when the test result will be available
- The probability of a positive result
- The significance of both a negative and a positive result
- What will happen if the result is positive?

3.4.2 Waiting period prior to the examination

The consequences of the waiting period between the invitation and the screening examination have not previously been studied in a screening programme for either Type 2 diabetes or any other chronic diseases of a non-malignant nature. The existing knowledge about the consequences of the waiting period derive from studies of screening for breast cancer (57) (1b). These report that during the week up to the screening examination, 18% suffered from sleep disturbance, 16% felt apprehensive, 13-14% had difficulty in relaxing or concentrating, 12% felt irritable, and 7% had difficulty in feeling happy. The reported changes in behaviour occurred particularly in women who were the most apprehensive or depressive at the examination. The study is based on two psychometric measurements, one before and one after the women were offered screening. The study confirms that the offer affects a relatively large proportion, and that there are measurable effects at the psychological level during the waiting period in the group that has chosen to undergo examination. Likewise the study confirms that particularly vulnerable groups exist. Despite the fact that Type 2 diabetes is not regarded as a “malignant” disease, there is reason to believe that an offer for screening for Type 2 diabetes and the subsequent waiting period up to examination might also have consequences of psychological and social character.

3.4.3 The screening examination and the following diagnostic examination

As mentioned, screening for Type 2 diabetes can consist of a self-completion questionnaire on risk factors or a blood glucose measurement taken at a random time of the day at the general practitioner’s. The advantage of these methods is that they are cheap, simple and can be undertaken by the patient himself or by his general practitioner. As described earlier, however, the disadvantage is that they cannot reliably categorise the examined persons as “truly ill” and “truly healthy”. Simple screening methods can yield a relatively large group of persons who will have to undergo further examination in order to be declared ill or healthy. The persons declared “potentially ill” who are subsequently declared healthy will certainly be affected by the situation, which might entail consequences of a psychological and/or social nature. There are no studies available that shed light on the psychological and social consequences of a false positive answer from screening for Type 2 diabetes, however. With other disease groups it has been reported that women feel greater apprehension if they have to undergo a second examination in connection with screening for breast cancer. It is unsure, though, how intense and long-lasting the effect is (58) (1b). Similarly, it is reported that a false positive diagnosis can subsequently lead to insecurity and worry (58) (1b). A Danish review (59) (1a) concludes, however, that it is difficult to demonstrate significant general changes in psychological reactions in groups of false positive, but that a particularly vulnerable group of persons probably exists for whom the consequences will be more severe. A study (60) (2b) concerning women taking part in screening for cervical cancer has demonstrated four psychologically related variables able to predict a high level of anxiety: 1) Former mental problems, 2) Low self-esteem, 3) Low score for extroversion, and 4) High score for neurotic personality type.
The advantages of using a simple and cheap screening method should therefore be weighed against the possible disadvantages concerning the proportion of persons who are initially declared “potentially ill” and later on “healthy”.

No studies concerning Type 2 diabetes or other diseases have been identified, however, that have tested different diagnostic examination procedures in a randomised design with the aim of describing and comparing psychological and social consequences. We are thus unable to provide the right solution, but can draw attention to the problem area. It will be essential to perform studies of the consequences of different screening procedures for the psychological and social welfare of the screened persons. One Danish study (previously mentioned in this chapter) (37) includes assessment of the psychological and social consequences of a screening model that uses questionnaires to select a high-risk population for further investigation.

3.4.4 Repetition of the screening programme

From the patient perspective, repeated screening of the same population at intervals of a few years will particularly affect those persons who test false negative and those who test false positive. The initially false negatives will very likely test true positive at a second examination, which can therefore be considered a positive consequence of repetition. A negative consequence is that the risk of healthy individuals testing positive (false positive) increases steadily with the number of screening repetitions. A review of the cumulated risk of receiving a false positive diagnosis upon mammography screening in the USA demonstrated a 40% risk of receiving a false positive answer once if screening was undertaken once a year for 10 years (61) (2b). Even though screening for Type 2 diabetes will not necessarily be undertaken that often, the risk of testing false positive at repetitions will be such that it has to be taken into account when deciding upon screening frequency.

3.4.5 To be declared “ill”

To be diagnosed as having Type 2 diabetes can be experienced very differently. In the study where people with newly diagnosed Type 2 diabetes were interviewed (55), some of the involved persons were reportedly satisfied that the disease was detected so early that something could be done about it as they experienced a rapid improvement in blood glucose level. Other interviewees told about life situations characterised by poor compliance with medical advice, increased apprehension and stress and denial of the disease.

To receive the diagnosis Type 2 diabetes can also change other people’s ideas of what the person is able to do, what he may do and may not do, and still others may believe that it is the patient’s own fault that he is ill. This stigmatisation can presumably lead to:

- Discrimination at the work place
- Discrimination as a consequence of the blame for the disease being placed on the person himself
- Monitoring of e.g. whether the one part in a marriage observes dietary restrictions, can create imbalance in the relationship
- Overprotection by family and friends.

The extent of the consequences of stigmatisation has not been investigated, however.

Other consequences of becoming labelled as ill can be that it might influence the possibilities for obtaining life insurance (62) (5), which might entail worries for the future prospects of the patient’s spouse and children.

3.4.6 Non-responders

In general, we know very little about the persons who do not accept the offer of being screened. A study of persons who did not participate in a screening for cervical cancer in Denmark showed that the group of women who were never examined more rarely used their general practitioners than the group of women who were examined (63) (3b). The “never” group more often lived alone and more often had never been pregnant, but there was no overrepresentation of cancer risk factors. A Swedish study made corresponding findings in a group of women who did not accept the offer of mammography. To be single or unemployed were the only socio-demographic predictors for not participating. A larger proportion of the “non-participants” had not seen a doctor for five years, had never taken contraceptive pills or other hormone drugs, had never been screened for cervical cancer, never drank alcohol, but smoked more often (64) (3b). Nothing is known about which groups do not accept offers of screening for Type 2 diabetes, however. It would be valuable to investigate whether the risk of developing Type 2 diabetes is higher in the group of non-responders.
Subconclusion

- Little has been reported about the ethical, psychological and psychosocial consequences of screening as specifically related to diabetes, and decisions about screening must therefore largely be based on extrapolation from experience with other disease categories.
- The majority of published studies are based on other countries and other health services than the Danish, which limits their generality. Moreover, cultural factors must be presumed to be of significance for the psychological and social consequences.

3.5 Organisation of early diagnosis and screening

Requirement 3: Diagnostic and treatment facilities have to be available:
Most diagnosis and treatment of patients with Type 2 diabetes presently takes place in general practice. The role of the general practitioners will remain a central consideration when planning screening and diagnosis. Screening might very well be organised in such a way that the first step in the form of a risk assessment is made without the assistance of doctors or other health personal. Thus the persons in the target group can themselves undertake the first step, e.g. by using a questionnaire with associated risk scoring system. In the next step, however, in which a detected risk has to be disproved or confirmed, it will be necessary for persons in the risk group to contact the health service to have a blood glucose measurement made. It will be possible to take the necessary blood samples for diagnostic purposes in general practice, after which they are either analysed there or sent to a central laboratory. In principle, the resources are thus available, but the task will entail a workload for case finding and diagnosis in general practice that will have to be taken from other ongoing activities in general practice.

Requirement 10: Screening efforts have to be a continuous process and not a one-off event:
The purpose of repeating a screening is to continuously identify new cases of disease. From other screening programmes (e.g. screening for cervical cancer) it has been shown that screening can be undertaken as a continuous process based in general practice and with the screening activity being monitored through central registration at County level. A corresponding system could in principle be established to ensure a screening programme for diabetes. Basing the first step of the screening programme on a self-completion questionnaire will hamper analysis of those who do not progress to the next stage of screening as there can be two reasons for not visiting one’s general practitioner, namely that the risk score is low (that the person is not at risk), or that the person does not want to participate in the programme. It will not be possible to directly differentiate between these two groups. No studies are presently available that can contribute to our knowledge about the frequency with which screening should be undertaken. Most national and international programmes recommending screening recommend intervals of 3-5 years. No studies are available showing that exactly these intervals are decisive, however.

The costs of each newly diagnosed case of disease are far higher for the second and the subsequent screening rounds than for the first one. This is due to the first round catching all persons with undetected disease irrespective of the duration of the disease (the prevalence group). This “depletes” the population of persons with undetected Type 2 diabetes. In the second round persons are identified who were healthy the first time they were screened, but who have now got the disease (incident cases). As this number is small, but the costs of carrying out the screening are unchanged, the costs per newly detected Type 2 diabetes patient will increase significantly.

Requirement 14: Detailed descriptions of organisation, management, resources, education and patient information have to be available:
Most contact between the Danish population and the health service takes place through general practice, which is in good accordance with the principle that examination and treatment should be undertaken at the lowest effective care level (LECL). Similarly in accordance with the LECL principle the general practitioners carry out most of the examinations and the major part of the treatment without this entailing contact between the patient and the remainder of the health service. A study of the disease pattern in general practice thus shows that on any given day, 90% of all contact between patients and general practice does not result in referral to a specialist or hospital (65).

Approximately 98% of the Danish population have group 1 health insurance and are thus registered at a certain general practice of their choice in the local area. Often the members of a family are registered at the same practice for many years. Through his patient records and knowledge of his patients the general
practitioner therefore possesses a comprehensive knowledge of their health and social conditions, a knowledge that can be utilised in connection with an assessment of the patients' risk of having Type 2 diabetes.

Screening can be organised without the involvement of general practice. The persons in the target group can either be directly invited or can be encouraged by means of public campaigns to contact a central laboratory with a view to screening and diagnosis. As is apparent from Section 2.5.2, the socio-economic analysis of screening and diagnosis does not unambiguously point to either general practice or central laboratories. Moreover, the literature search did not reveal any studies that favour one choice rather than the other. Very important reasons should therefore exist if general practice is to be passed over in favour of a central laboratory. Similarly, concrete conditions will have to determine whether a model is chosen where the whole diagnostic examination is carried out in general practice through the analysis of whole blood, or a model where the general practice centrifuges a blood sample and forwards the plasma for analysis at a central laboratory. A final possibility is that the general practitioner carries out risk assessment of the patient and if necessary refers the patient to a central laboratory for blood sampling and analysis.

Opportunistic screening only makes sense in connection with general practice as this is the part of the health service to which the population predominantly turns with their health problems. An analysis of the health insurance payment data for general practices in Aarhus County shows that during the three-year period December 1998 to November 2001, a very large proportion of the population was in contact with general practice in the form of a consultation with their general practitioner. In all one-year age groups from 0 to 88 years the proportion having at least one consultation with their general practitioner during normal surgery hours was between 89% and 97%. On this background an opportunistic screening strategy based on general practice must be regarded as technically feasible.

As is apparent from the introduction to this chapter, one of the criteria for instigating screening is that it is continuous and not a one-off event. Due to the pattern of the population's contact to general practice it will be possible to offer screening at intervals of three years and upwards to a very large proportion of a given target group without any other form of invitation than that the general practitioner can give in connection with the patients contacting the doctor for other reasons. To ensure that the offer of screening is repeated within given intervals, computer-based administrative systems can be used. These can register when a given patient has undergone diagnostic examination without this having resulted in a diagnosis. The system will subsequently be able to warn the general practitioner that a given patient should be offered screening at his next visit. Most of the computer systems presently used in general practice probably already enable this to be done. If not, registration can be made in the County computer systems used for managing the payment of physicians' fees.

The main barrier to the use of general practice as a screening place is the considerable heterogeneity between the different practices as regards organisation, professional spheres of interest, facilities (including laboratory facilities) and attitude to screening. As a coordinated screening effort depends on uniformity of the offers made to the individual persons, significant educational efforts will need to be directed at the primary sector. The nationwide agreement between the Health Insurance Negotiation Committee and the College of General Practitioners include provisions promoting further education and quality assurance in general practice. Economic resources are allocated to a nationwide further education fund that the general practitioners can draw on, as well as to a quality development pool in the individual Counties that can support initiatives on the quality and further educational fronts in general practice. In all Counties, cooperation exists between the Practice Committee for the general practitioners and the management of the County health services on these initiatives.

In connection with a decision by a County to instigate systematic screening for or just intensified case finding of Type 2 diabetes an obvious possibility will be to use the contractual cooperation on further education and quality assurance to support the selected programme. Both organisation and management of the programme can take place within the context of this cooperation, as can the planning and implementation of information about and training in the programme.

**Subconclusion**

- Diagnosis and treatment facilities exist in both the primary sector and in special outpatient clinics, and there are no major economic differences between screening/diagnosis in the primary and secondary sectors. The frequent and close patient contact in general practice speaks in favour of the activity primarily being assigned to general practice, but there is a lack of studies documenting that opportunistic
screening can actually be carried out in general practice. If such screening were undertaken, moreover, time and resources would have to be made available in general practice, and an analysis should be made of which activities would have to bear the costs of intensified efforts on the diabetes front in general practice (4).

If one examines experience from other screening programmes there is reason to believe that screening can be carried out in general practice – provided that relevant monitoring systems are established to monitor the screening activities (5).

If the decision is made to implement screening or more active and systematic case finding in general practice, consideration should be given to how this can best be coordinated with other screening and case finding activities, especially within the cardiovascular area, e.g. screening for hypertension and dyslipidemia (5).

3.6 Health economic assessment of screening strategies

Requirements 9 and 13: The costs of case finding have to be reasonable in relation to the health service’s total expenses, and the health economic consequences of screening have to be described:

This section describes the current knowledge on the cost-effectiveness of screening for Type 2 diabetes based on foreign economic models. No Danish cost-effectiveness analyses of screening for Type 2 diabetes have been made, and it has been beyond the temporal and economic framework of this HTA report to perform such analyses. Results of foreign economic analyses cannot be directly transcribed to Danish conditions due to differences in treatment practice and costs. However, foreign analyses can provide an indication of the relationship between costs and effects. Existing foreign analyses of diabetes screening are therefore examined here.

An assessment is made of the direct costs (operating costs) in the public health service for:

- Population screening based on an initial risk assessment through questionnaires
- Opportunistic screening in general practice.

3.6.1 Cost-effectiveness of screening for diabetes

A literature search identified three studies of direct relevance (Table 3.6.1.1). An Australian study (66) shows that the costs per newly diagnosed Type 2 diabetes patient are approx. 80% higher with population screening based on fasting blood glucose than with corresponding opportunistic screening, where diabetes is tested for in connection with a consultation for another purpose. As expected, the costs per newly diagnosed case are lower if screening is limited to risk groups such as overweight persons.

The aim of the CDC model – another American study – was considerably more ambitious. With the aid of a computer simulation model, existing knowledge from epidemiological and controlled clinical investigations was used to estimate the consequences of screening for duration of life, quality of life and costs during the remainder of the patients’ life (67). The simulated intervention consisted of a single opportunistic screening of all persons aged 25 years and over. The model calculations show that the cumulative incidence of terminal renal failure, blindness and amputations can be reduced by 22-35%, which means that quality of life is improved. The duration of life is only marginally affected, though.

As in other health economic analyses, the cost-effectiveness has been calculated as costs per gained life-year and costs per gained quality-adjusted life-year (QALY)⁴, respectively. The costs per gained life-year were approx. USD 236,000 (DKK 1,914,000)⁵, and the costs per gained quality-adjusted life-year were approx. USD 57,000 (DKK 462,000) with the base scenario. Despite the lower prevalence of undetected diabetes it was more cost-effective to screen younger persons than older persons (Figure 3.6.1) – primarily due to deferment of complications and thereby improved quality of life, and less due to prolongation of lifetime. Apart from the fact that the study is based on American costs and clinical practice, there are a number of other limitations in the model that necessitates that the results should be interpreted with caution (Table 3.6.1.1). One of these limitations is that the CDC model (Table 3.6.1.1) does not include effects on cardiovascular diseases. Another American calculation shows that if one is willing to make more optimistic assumptions – 30% reduction in cardiovascular risk and 30% lower costs for control and treatment of diabetes –

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⁴ The quality-adjusted life-year is a measure of health that for each year of life is assigned a weight in the range 0 to 1 corresponding to the health-related quality of life in that period. The weight 1 corresponds to the best possible state of health, while the weight 0 indicates death.

⁵ The exchange rates used are the average of the rates set by the National Bank in the period 2/1.2002-21.8.2002: USD 811 and GBP 1189.
then screening becomes cost-saving (68). On the other hand, cost-utility models have generally been criticised for being able to exaggerate the cost-effectiveness of interventions that improve quality of life (69)6.

### Table 3.6.1.1
Foreign cost-effectiveness analyses of screening for Type 2 diabetes

<table>
<thead>
<tr>
<th>Aim</th>
<th>Method</th>
<th>Number + country</th>
<th>Validated method</th>
<th>Results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Victoria Easton og Seagal 1998 [66]</td>
<td>Estimate costs per newly diagnosed Type 2 diabetes patient (opportunistic screening)</td>
<td>Model</td>
<td>Victoria, Australien</td>
<td>Opportunistic screening is cheaper than population screening (cost/ newly diagnosed). Costs per newly diagnosed lower in risk groups (overweight, Italian)</td>
<td>May be considered an illustrative calculation example.</td>
</tr>
<tr>
<td>METASTAR Lee et al. 2000 [68]</td>
<td>Estimate costs or savings entailed by “community screening” of persons aged 65 years and over</td>
<td>Uses CDC model + assumptions about CVD effect and costs</td>
<td>Wisconsin, USA 12,357 offered screening, 826 screened</td>
<td>Assumptions about CVD effect based on UKPDS. Assumes about costs</td>
<td>If one assumes a 30% reduction in CVD and assumes that treatment costs are 30% lower for persons identified by screening, then screening is cost-saving.</td>
</tr>
</tbody>
</table>

**FIGURE 3.6.1.1.** Impact of age on the cost-effectiveness of opportunistic screening in the USA

![Graph showing impact of age on the cost-effectiveness of opportunistic screening in the USA](image)

Source: CDC Diabetes Cost-Effectiveness Group (67).

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6 Here and below we evaluate and use cost-utility analyses performed according to two common methodological standards. As in other areas of health economics, methodology is continually being discussed. One example of this is the cited article by Erik Nord. It is outside the scope of the present report to go into methodological discussions.
A simpler Australian model does not include cost-effectiveness assessments, but alone tries to describe the significance of central parameters in determining whether or not screening does more good than harm (70). From this analysis two interesting circumstances can be deduced: If the fact of being diagnosed with Type 2 diabetes and subsequently treated entails even a minor fall in quality of life, this might mean that screening overall does more harm than good, in which case cost-effectiveness calculations become irrelevant. Conversely, if screening (and subsequent treatment) has a positive effect on cardiovascular diseases, this effect might very well turn out to be considerably greater than the effect on blindness and renal and neurological complications (measured in quality-adjusted life-years).

A Danish study of the cost-effectiveness of screening for Type 2 diabetes has been initiated, but the findings will not be available until in 6-7 years time (37).

**Screening and/or other diabetes interventions – how do we get most for our money?**

This question cannot be answered unambiguously with the present knowledge. The question is nevertheless very relevant because incomplete knowledge does not free us from the responsibility of deciding on where the limited economic resources are best used within the diabetes area.

The CDC model showed that the cost-effectiveness of screening is exponentially dependant on age and hence declines markedly when screening persons aged over 55 and 65 years, respectively (Figure 3.6.1).

Another simulation study of a population-based cohort (NHANES III) shows that by far the majority of all cases of blindness arise in the persons who get Type 2 diabetes at an relatively early age and have poor blood glucose regulation at the onset of diabetes (71). The model was used to analyse the expected effects of screening, of a hypothetical, improved treatment of persons with poor blood glucose regulation that ensures that all patients fall to an HbA1c value of 9%, and of a combination of these two elements. It is estimated that roughly speaking, a combination of these two interventions would halve the number of persons who become blind. Screening alone only accounts for 7% of this effect, whereas improved treatment of persons with poor blood glucose regulation accounts for 65%. The authors are of the opinion that future efforts in the area should be concentrated on improving diabetes treatment in known diabetes patients who have developed Type 2 diabetes early and whose blood glucose regulation is poor. If the treatment of this group could be improved, it would concomitantly enhance the effect of screening.

Another alternative to screening is to spend money on intensive treatment of all Type 2 diabetes patients with the aim of normalising the blood glucose regulation as much as possible. Using fundamentally the same simulation model as in the CDC study and comparable assumptions the cost-effectiveness of intensive blood glucose treatment is estimated to be approx. USD 16,000 (DKK 130,000) per quality-adjusted life-year (72) and in a further developed model (73) to be approx. USD 41,000 (DKK 330,000). This is on par with the modelled cost-effectiveness of a single opportunistic screening of persons between 25 and 54 years of age, but considerably more cost-effective than opportunistic screening of persons aged 55 years and over (67).

### 3.6.2 Costs of screening in Denmark

Based on the discussion of the relative advantages of different screening methods a closer examination is here made of the economic consequences of two concrete screening programmes for persons aged 40-70 in Denmark, corresponding to the strategy used in an ongoing Danish study (37).

**Population screening based on preliminary risk assessment using questionnaires**

This screening programme consists of a two-phased risk assessment, the first phase of which was a questionnaire sent by post to all persons aged 40-70. Persons in whom this reveals an increased risk of diabetes are encouraged to contact their general practitioner. The second part of the risk assessment is a blood sample collected by the general practitioner. The blood sample is tested for capillary blood glucose and glycosylated haemoglobin (HbA1c). If the blood samples indicate that the patient is at increased risk, diagnostic examination is instigated in general practice (diagnostic Model 2 in Section 2.5). It is estimated that such a programme can be expected to identify 1-2% of the population as persons with Type 2 diabetes, corresponding to approx. 20,000-40,000 persons.

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7 Unfortunately, there are no quantitative studies of how health-related quality of life is affected by the fact that a person is diagnosed with Type 2 diabetes and placed under treatment. Goyder and Irwig (70) claim that this has a negative effect on quality of life. This can be explained by dislike of "labeling" and treatment, but conversely it can also be argued that blood glucose-regulating treatment will enhance quality of life by alleviating symptoms of diabetes.

8 This assessment is based on preliminary figures from the ADDITION study.
The costs of one screening round are calculated to be approx. DKK 71 per person and approx. DKK 140 million for the whole 40-70-year age group in Denmark (Table 3.6.2.1). The cost estimate is based on the assumption that approx. 25% of the population will be identified by the questionnaire as having a risk score sufficiently high that they should report to their general practitioner, but that only approx. 60% of these will actually do so\(^9\). Thus approx. 15% of the population will visit their general practitioner to participate in phase 2 of the risk assessment. Approximately half of these (7.5%) will have to proceed to diagnostic examination\(^10\).

### TABLE 3.6.2.1
Population screening
Costs for a single round of screening (DKK)

<table>
<thead>
<tr>
<th>Percentage encompassed</th>
<th>Unit cost</th>
<th>Cost per person in the screening group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Questionnaire by letter</td>
<td>100%</td>
<td>12</td>
</tr>
<tr>
<td>Screening at general practitioner</td>
<td>75%</td>
<td>259</td>
</tr>
<tr>
<td>Diagnostic examination</td>
<td>7.5%</td>
<td>270</td>
</tr>
<tr>
<td>Total per person in screening group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost for all aged 40-70 years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Opportunistic screening in general practice**

This screening programme is based on the general practitioners assessing the risk of 40-70-year-old persons having Type 2 diabetes in connection with a consultation for other reasons. If the general practitioner assesses that a person has an increased risk, diagnostic examination is initiated (diagnostic Model 2 in Section 2.5).

Based on data from the Health Insurance Register\(^11\) it has been calculated that approx. 92% of persons aged 40-70 years have one or more consultations at their general practitioner during a three-year period. It is estimated that 25% of these persons have a risk profile suggesting that they should undergo further diagnosis. However, it is unrealistic to expect that the general practitioners will perform a risk assessment of them all, just as it must be expected that part of them will not want to undergo actual diagnostic examination. It is therefore assumed that only 25-50% of those whose risk profile suggests that they should undergo further diagnostic examination will actually do so.

Based on these estimates and assumptions the total annual costs for opportunistic screening of 40-70-year-old persons can be calculated at between DKK 10 and 21 million (Table 3.6.2.2). During the first three years, 92% of the age group will have had the chance to be screened, but only 6-12% can be expected to have undergone diagnostic examination. The annual costs after the first three years will among other things depend on to what extent the general practitioners choose to repeat the screening/risk assessment of persons who have already undergone either risk assessment or diagnostic examination once without diabetes having been detected.

### TABLE 3.6.2.2
Cost estimates for opportunistic screening
Direct costs in the health service (DKK)

<table>
<thead>
<tr>
<th>Proportion of the whole age group that undergoes diagnostic examination</th>
<th>Costs/person who undergoes diagnostic examination</th>
<th>Costs/person in the target group</th>
<th>Costs for all aged 40-70 years per screening round (3 yr)</th>
<th>Annual costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low estimate</td>
<td>6%</td>
<td>270</td>
<td>30,000,000</td>
<td>10,000,000</td>
</tr>
<tr>
<td>High estimate</td>
<td>12%</td>
<td>270</td>
<td>63,000,000</td>
<td>20,000,000</td>
</tr>
</tbody>
</table>

Calculation assumptions: a) 92% of the target group attend a consultation within three years. b) 25% of these have a risk profile indicative of a need for diagnostic examination. c) Of the persons who fulfill both a) and b) 25% (low estimate) or 50% (high estimate) actually undergo diagnostic examination.

**Costs per newly detected diabetes patient**

Based on the calculated costs for population screening (Table 3.6.2.1) and the expected proportion of the screened population that will be identified as persons with Type 2 diabetes (1-2%), the costs per newly detected Type 2 diabetes patient will be DKK 3,500-7,000 for the first round of a population screening. Based on preliminary prevalence figures from the INTER99 study it is estimated that upon repeated screening

\(^9\) This is based on experience in INTER99.
\(^10\) Based on unpublished data from the INTER99 and ADDITION studies.
\(^11\) Data made available by the Ministry of the Interior and Health, 7th Health Division.
the number of non-diagnosed diabetes patients in the age group will fall to a stable level of the order of magnitude of one sixth of that detected in the first screening round. As the costs of undertaking screening will only change relatively little, the costs per newly detected patient with Type 2 diabetes will increase correspondingly (cf. Section 3.5 – requirement 10).

There are no reliable figures for how many persons with Type 2 diabetes will be detected by opportunistic screening. A rough estimate of this number is necessary if it is to be possible to assess whether opportunistic screening can be expected to be more or less cost-effective than population screening.

Based on preliminary, unpublished figures from the INTER99 and ADDITION studies it has previously been estimated that approx. 7.5% of the screened population undergoes diagnostic examination, and that 1-2% of the screened population will be identified as persons with Type 2 diabetes. This corresponds to 13-27% of the persons who undergo diagnostic examination, having Type 2 diabetes.

In the following it is estimated that persons who undergo diagnostic examination in opportunistic screening have the same probability (13-27%) of being diagnosed with Type 2 diabetes as persons undergoing diagnostic examination in a population screening programme. The preliminary phases of both a population screening programme and an opportunistic screening programme aim to identify persons with a higher probability of having diabetes than average persons. This is the fundamental rationale for the above assumption. There are indications for both a higher and a lower probability in an opportunistic screening programme. In favour of a lower probability in the opportunistic group is the fact that the selection of high-risk individuals by the general practitioner might be less effective than the evidence-based, systematic selection in population screening. In favour of a higher probability in the opportunistic group is the fact that the general practitioner has the possibility to convince persons at risk who in the population screening might refrain from contacting their general practitioner, and that the general practitioners perhaps unconsciously focus on persons with a particularly high risk, such as extreme overweight.

Based on the above-mentioned assumption, the costs per identified Type 2 diabetes patient can be calculated for four scenarios (A-D) which combine a high and a low estimate of the proportion of persons who will undergo diagnostic examination in the opportunistic screening (6 and 12%, respectively), with a high and a low estimate of the proportion of persons who will undergo diagnostic examination and who prove to have Type 2 diabetes (13 and 27%, respectively). If the assumption is correct, the costs per newly detected Type 2 diabetes patient during a single three-year round of opportunistic screening will be approx. DKK 1,000-1,900, and the screening round will identify an estimated 16,000 to 65,000 Type 2 diabetes patients (Table 3.6.2.3).

If the assumption holds, a single opportunistic screening round will be more cost-effective than a single population screening round. The probability that persons who undergo diagnostic examination in the opportunistic screening programme will be diagnosed with Type 2 diabetes will have to be considerably lower than in the population screening programme before it changes this conclusion.

### TABLE 3.6.2.3

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Direct costs in the health service</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Proportion of the age group that undergoes diagnostic examination</td>
<td>6%</td>
</tr>
<tr>
<td>Proportion of persons that undergo diagnostic examination and who have diabetes</td>
<td>13%</td>
</tr>
<tr>
<td>Proportion of 40-70 age group who are diagnosed with diabetes</td>
<td>0.8%</td>
</tr>
<tr>
<td>Number of detected diabetes patients</td>
<td>16,143</td>
</tr>
<tr>
<td>Total costs for 3-yr screening round (DKK)</td>
<td>31,000,000</td>
</tr>
<tr>
<td>Costs per newly detected Type 2 diabetes patient (DKK/person)</td>
<td>1,900</td>
</tr>
</tbody>
</table>

The assumption on which the above estimates are based is that a person who undergoes diagnostic examination in the opportunistic screening campaign has the same likelihood of being diagnosed with Type 2 diabetes as a person from the population screening programme who undergoes diagnostic examination. The four scenarios A-D combine a high and a low estimate for the percentage of persons who undergo diagnostic examination and who turn out to have Type 2 diabetes (13% and 27%, respectively).

### Costs for treatment of newly diagnosed Type 2 diabetes patients identified through screening

The annual costs for treatment and regular control of a Type 2 diabetes patient are calculated to be approx. DKK 4,900 (Chapter 5; Table 5.4.1). Given that a single population screening round among Danes aged
40-70 will identify approx. 20,000-40,000 Type 2 diabetes patients (1-2%), the indirect costs for treatment and regular control can thus be estimated to lie between DKK 100 and 200 million per year for a period that will be shorter than the probable latency of 5-11 years (23, 26). Similarly, a single opportunistic screening round that identifies somewhere between 16,000 and 65,000 persons with Type 2 diabetes can be estimated to entail annual costs for treatment and regular control of between DKK 80 and 320 million. These figures are not precise estimates. The real additional costs might be less if some of the newly detected Type 2 diabetes patients are already being treated for hypertension, or if quite newly detected patients are treated less intensively than the average patient. Conversely, the treatment costs will be greater if intensive polypharmacy is used.

As it has not been possible to estimate how many new Type 2 diabetes patients might be identified by opportunistic screening, it is not possible to calculate corresponding figures for this screening model.

### 3.6.3 Overall assessment of costs and cost-effectiveness of screening for Type 2 diabetes in Denmark

Final documentation for the clinical effect of screening and subsequent treatment of patients identified through screening is lacking, even though such an effect can be presumed from epidemiological studies (Section 3.3). The psychological and psychosocial consequences of screening are very poorly described with respect to diabetes screening (Section 3.4). Foreign economic models show a cost-effectiveness in the order of magnitude of approx. DKK 500,000 per gained quality-adjusted life-year (QALY) or even cost savings if one is willing to make more optimistic assumptions (Section 3.6.1). Due to differences in population composition, treatment patterns and cost structures, however, these figures cannot be directly transferred to Danish conditions. Cost calculations for Denmark show that the price of finding a single person with Type 2 diabetes will be DKK 3,500-7,000 with a single population screening (first round), and presumably somewhat lower, in the order of magnitude of DKK 1,000-1,900, with a single opportunistic screening.

The costs of finding a single person with Type 2 diabetes must be considered to be relatively limited, especially with opportunistic screening. Weighing all the available knowledge, however, it must be concluded that due to uncertainty as to improvement of the prognosis, possible psychological effects of screening and increased treatment cost, it is not presently possible to determine whether or not screening for Type 2 diabetes in Denmark will be cost-effective.

**Subconclusion**

- Based on the information available it is not possible to determine whether screening for Type 2 diabetes in Denmark will be cost-effective.
- A single population screening round of all Danes aged 40-70 years is estimated to cost approx. DKK 140 million and identify 20-40,000 persons with Type 2 diabetes. The costs per Type 2 diabetes case detected are estimated to be DKK 3,500-7,000 in the first screening round, but will be up to approx. six-fold higher in subsequent screening rounds.
- A single opportunistic screening of the same age group over a 3-year period is estimated to cost DKK 31-63 million and identify between 16,000 and 65,000 persons with Type 2 diabetes. The costs per Type 2 diabetes case detected are estimated to be in the order DKK 1,000-1,900 in the first 3-year screening round. It is not possible to calculate corresponding figures for subsequent opportunistic screening rounds.
- Based on the available foreign model analyses it is expected that screening of a younger group, for example persons aged 25-44, will be considerably more cost-effective than screening of the 40-70 age group.

### 3.7 Conclusions and recommendations

#### General

- The aim of this chapter has been to carry out an HTA of the available evidence for screening for Type 2 diabetes based on the criteria described by Wilson and Jungner with subsequent additions.
- Type 2 diabetes is presently a widespread disease that has considerable consequences for the patient, the health service and society. One in two patients suffer complications of the disease at the time the diagnosis is made. There is a latent period of several years between the time the disease arises and its clinical diagnosis. All these conditions speak in favour of screening for Type 2 diabetes (1b).
Various validated methods are available that can be used to screen for Type 2 diabetes. Most tests only entail minimal physical discomfort and should therefore be acceptable. All suffer from a high degree of both false negative and false positive test results, however, depending on what cut-offs are selected for the individual test (2b).

Very little is known about the effect of screening in the form of a possible improvement of the prognosis through screening and earlier intervention (intensive treatment and prevention of complications), and assessments of such an effect must therefore be based on extrapolation of results from studies encompassing patients diagnosed clinically. As these patients must be assumed to have severe symptoms and a more serious disease state, such extrapolation is not unproblematic.

Mathematic simulation models are available that can estimate the probable effect of screening and early intervention. These show that it is expensive and that the costs per prevented serious complication are great and very uncertain (3b).

Studies are available showing that treatment has a positive effect in patients with newly detected diabetes where the diagnosis is based on the presence of symptoms (not screening) (1a).

Population-based screening for Type 2 diabetes involving blood sampling in the first step of the screening strategy is very cost-heavy and an organisationally very demanding task.

Based on the information available it is not possible to determine whether screening for Type 2 diabetes in Denmark will be cost-effective.

A single population screening round of all Danes aged 40-70 years is estimated to cost approx. DKK 140 million and identify 20-40,000 persons with Type 2 diabetes. The costs per Type 2 diabetes case detected are estimated to be DKK 3,500-7,000 in the first screening round, but will be up to approx. six-fold higher in subsequent screening rounds.

A single opportunistic screening of the same age group over a 3-year period is estimated to cost DKK 31-63 million and identify between 16,000 and 65,000 persons with Type 2 diabetes. The costs per Type 2 diabetes case detected are estimated to be in the order DKK 1,000-1,900 in the first 3-year screening round. It is not possible to calculate corresponding figures for subsequent opportunistic screening rounds.

Based on the available foreign model analyses it is expected that screening of a younger group, for example persons aged 25-44, will be considerably more cost-effective than screening of the 40-70 age group.

Based on the above conclusions, general screening for Type 2 diabetes cannot be recommended due to the associated costs and the uncertainty about a treatment effect (B).

Treatment has a documented effect in patients with clinical symptoms, and these patients should be identified as early as possible through intensified case finding (A).

Patients in whom the presence of diabetes has a marked impact on the recommended treatment regimes (type and intensity) should be systematically screened for diabetes (e.g. patients with known heart disease, hypertension, dyslipidemia) (B).

As there is a pronounced lack of knowledge about the effects of early case finding/screening for Type 2 diabetes, the Project Group recommends planning and carrying out a trial of “intensified case finding in general practice” in one or several counties in order to assess the feasibility, the effect in the form of the number of newly diagnosed Type 2 diabetes patients and the costs (total and per diabetes patient) (B).

Until evidence is available indicating that screening should be implemented, efforts should focus on optimisation and quality assurance of the existing clinical case finding (through education, clinical guidelines, optimisation of apparatus) and on optimisation of the treatment possibilities for patients with known Type 2 diabetes (A).
The current background for screening and intensive treatment is presently being evaluated. If these studies should show a marked effect of screening and early, intensive treatment, consideration should be given to whether screening for Type 2 diabetes should be offered to the Danish population. However, an analysis should be made from the organisational, economic and patient perspectives of whether a future screening programme should be integrated in a broader programme encompassing diabetes, cardiovascular disease and factors encompassed by the metabolic syndrome. Such a programme could more rationally identify individuals at high risk of developing not only diabetes, but also cardiovascular disease – and hence individuals who could benefit from screening and treatment.
4 Non-pharmacological treatment of Type 2 diabetes

Type 2 diabetes is a lifestyle disease that arises when genetically disposed individuals become overweight and physically inactive. There is thus a direct relationship between the number of overweight persons in a society and the prevalence of Type 2 diabetes.

Approximately 80% of all Type 2 diabetes patients are overweight. The most rational prevention and treatment of Type 2 diabetes is therefore lifestyle changes with a view to achieving a weight loss and enhanced physical activity. It is worth noting that even a minor weight loss of approx. 5% has a marked effect on blood glucose regulation, which improves the lipid composition of the blood (the lipid profile) and reduces the blood pressure.

The present chapter assesses the dietary recommendations and the effect of dietary change, weight loss and exercise in the treatment of Type 2 diabetes. The main focus is on the significance of weight loss and on how weight loss can be achieved. Studies using pharmacological treatment to achieve increased weight loss in Type 2 diabetes patients will be discussed in the chapter on pharmacological treatment.

The active participation of the patient in the treatment of Type 2 diabetes is essential for its success, especially in relation to glycaemic regulation. Enhanced motivation and compliance through education of the patients has been one of the cornerstones of the treatment for many years. The effect of self-monitoring of blood glucose, “diabetes schools” and the effects of other forms of education of the diabetes patient (self care) on glycaemic regulation and on other variables included in the therapeutic goals will therefore be reviewed as well. The value of cessation of smoking and prophylactic screening for diabetic foot problems are also included in the present chapter. Non-pharmacological treatment of Type 2 diabetes is thus multi-factorial, and it is therefore difficult to judge the effect of the individual components of the treatment, e.g. exercise versus weight loss.

As mentioned in the conclusions, major lifestyle changes are often difficult to implement, and with some patients it will become evident after a short duration of treatment that lifestyle changes cannot be implemented, or that the therapeutic goals cannot be obtained without supplementary medication. In this situation the patient should not be followed for months without considering pharmacological treatment as this might expose the patient to unnecessary risk.

4.1 Diet

4.1.1 Treatment of Type 2 diabetes with dietary change

The evidence for the general dietary principles employed in the treatment of Type 2 diabetes is discussed first in this chapter followed by discussion of the significance of the diet for weight loss, treatment of raised blood lipids (dyslipidaemia), raised blood pressure (hypertension) and diabetic kidney disease (nephropathy). In a few cases the recommendations are based on consensus or ordinary “common sense”.

The objective of the dietary recommendations is:
- To achieve the therapeutic goals for blood glucose, lipids and blood pressure
- To treat overweight
- To improve health in general
- In the case of Type 2 diabetes patients treated with insulin or oral antidiabetics, which increase insulin secretion, to learn how treatment-related problems such as hypoglycaemia, acute illness and exercise-induced blood glucose problems are avoided and treated.

4.1.2 Dietary content of carbohydrates in Type 2 diabetes

One of the most discussed issues within dietary treatment has been what percentage and forms of carbohydrate Type 2 diabetes patients should best consume.

Traditionally, carbohydrates are subdivided into sugar (sucrose), starch and fibre. The recommendation is that approx. 50-55% of the total calorie intake should derive from carbohydrates, and that carbohydrates and
Diets with a low glycaemic index give little or no improvement in glycaemic regulation (1b). Different forms of carbohydrates do not seem to affect glycaemic regulation differently. It is the total amount of carbohydrate in the meal and not the type of carbohydrate that determines the magnitude of the glucose and insulin responses during the meal (74-90) (1b) (76, 83) (3b). This also applies when the insulin and glucose response is compared after intake of starch and sugar (77, 79-81) (1b). The above is only valid, however, when the diet stays within the recommendations for healthy food applying for the whole population. The effect of carbohydrates on the lipid profile in the blood has been a matter of discussion – both as regards how much carbohydrate it is appropriate to eat, and which types of carbohydrate it is optimal to consume. Studies of the effect on the blood lipids of a diet with a high versus a low glycaemic index (an expression of how much the blood glucose concentration increases after consumption of a meal) have yielded conflicting results (82, 84-90) (1b). Like the remainder of the population, Type 2 diabetes patients are encouraged to eat fibre from cereals, fruit and vegetables. Patients with Type 2 diabetes will have to consume very large amounts of fibre before it has an effect on glycaemic regulation and lipids – an amount which in many persons will entail unacceptable side effects (91, 92) (1b). In a meta-analysis of 67 controlled clinical studies a diet with an increased content of water-soluble fibre caused a fall in total cholesterol, LDL cholesterol and HDL cholesterol, while triglycerides remained unchanged (93) (1a). Meal frequency – three main meals or smaller meals with inter-meal snacks – does not affect the glucose, lipid and insulin responses (94, 95) (1b). Insulin-treated Type 2 diabetes patients are usually treated with an intermediate-acting insulin once or twice per day, possibly as a mixed preparation of short-acting and intermediate-acting insulin. No studies of insulin-treated Type 2 diabetes patients have shown that diets with high and low carbohydrate contents have different effects on glycaemic regulation. Part of the explanation for this is that it is the insulin dose and the insulin regimen that largely regulate the diurnal glucose fluctuations. Type 2 diabetes patients do not normally regulate their insulin dose daily depending on meal sizes and times. It is therefore recommended that the insulin-treated Type 2 diabetes patient should consume the same amount of carbohydrates daily, and that the meal times should be kept constant in order to reduce hyperglycaemia and avoid hypoglycaemia.

Glycaemic index

Glycaemic index was introduced by Jenkins and co-workers as a method for assessing how different foods affect the glucose response after a meal, e.g. how rye bread affects the glucose increase compared with an isocaloric amount of rice (96) (4). Tables indicating glycaemic indices are available, and these can be used in daily life as a rough guide. In practice, though, it has turned out that the glycaemic index of a mixed diet depends on many other factors, such as how the food is prepared, and the amount of fat and protein. Thus many foods with a high fat content have a low glycaemic index, while ordinary foods, which are recommended, such as bread and potatoes, have a high glycaemic index.

Nine studies involving Type 2 diabetes patients have compared diets with a low or high glycaemic index (82, 84-90) (1b) (83) (3b) for periods longer than one day. Four studies did not find any difference in the HbA1c level (82, 85, 86) (1b) (83) (3b), three studies found improved glycaemic regulation (expressed by fructosamine) on a diet with a low glycaemic index (87-89) (1b), while three studies did not find any difference in fructosamine (85, 86, 90) (1b). No difference in fasting glucose was found in eight of the studies, and in two studies the insulin levels did not differ (84, 86) (1b). The effect on lipids varied, without any certain improvement upon a diet with a low glycaemic index.

As mentioned above, the significance of the amount and type of carbohydrate for glycaemic regulation and lipid metabolism is a matter of discussion. The European Association for the Study of Diabetes (EASD) still recommends a diet with a low glycaemic index for Type 2 diabetes patients (97) (5). The opinion of the EASD is substantiated by the conclusions of a recent meta-analysis that a diet with a low glycaemic index improves HbA1c by around 0.4 percentage points as compared with a diet with a high glycaemic index (98) (1a). This is contrary to the recommendations of the American Diabetes Association (ADA), which are founded on the idea that it is the amount and not the type of carbohydrate that is decisive for the glucose and insulin response during a meal. Their argument is that even though there are reasons to believe that the blood glucose increase is less during a meal with a low glycaemic index, it is not reflected in a lower HbA1c value (99) (1b). The ADA instead recommends that the patient learns to “count carbohydrates”, and that emphasis is placed on weight loss via a hypocaloric diet in order to thereby improve glycaemic regulation.

Subconclusion

- Different forms of carbohydrates do not seem to affect glycaemic regulation differently. It is the total amount of carbohydrate in a meal that is of significance for the glycaemic response (1b).
- Diets with a low glycaemic index give little or no improvement in glycaemic regulation (1b).
Type 2 diabetes patients treated with a fixed daily dose of insulin (one- or two-dose therapy) should eat the same amount of carbohydrate each day (5).

Carbohydrates and monounsaturated fat should comprise 60-70% of the energy intake (5).

### 4.1.3 Sucrose
Sucrose is a naturally occurring disaccharide consisting of a glucose and a fructose molecule. Earlier dietary recommendations were very restrictive as to sucrose in that it was believed to aggravate the hyperglycaemia (blood glucose increase) after a meal. There is no scientific evidence for this assertion, however, as long as the amounts consumed are those recommended for a healthy diet in general. There is thus no evidence that sucrose in the food increases the blood glucose level more than an isocaloric amount of starch (74, 77, 79, 81, 100-102) (1b).

It is recommended that persons with diabetes only consume up to 25-30 g of sugar per day, and that this is distributed between the various meals of the day, with no more than 5 g sugar at a time. As an alternative to sugar, artificial sweeteners can be used. Artificial sweeteners do not cause a rise in blood glucose and are not transformed into energy to any great extent. Consumption of large amounts of sucrose can entail increased risk of caries. The sucrose intake should be limited in patients with high triglyceride levels. Soft drinks containing sucrose can be used for treating hypoglycaemia. The consumption of sucrose in soft drinks seems to dispose to obesity (103).

### 4.1.4 Fructose
Fructose, which primarily derives from fruit, vegetables and soft drinks, has been shown to reduce hyperglycaemia during a meal when substituting sucrose or starch as the carbohydrate source (74, 81, 105) (1b) (104) (4). Fructose is therefore a good sweetener in the diabetes diet. Large amounts of fructose (15-20%) in the daily energy intake, however, adversely affect the lipoproteins in the blood leading to an increase in LDL cholesterol and triglyceride (105-109) (1b) (106, 107) (3b) (108) (4).

### 4.1.5 Polyols
The consumption of polyols such as sorbitol, mannitol and xylitol seems to entail a lower glucose response than isocaloric amounts of fructose, sucrose and glucose (110-113) (3b) (110-115) (4). The probable explanation is that polyols are not absorbed until they reach the small intestines.

**Subconclusion**
- Sucrose does not increase postprandial hyperglycaemia more than an isocaloric amount of starch (1b).
- When sucrose is included in the diet, it should be as a substitute for other types of carbohydrates (5).
- Fructose reduces postprandial hyperglycaemia when included in the diet instead of sucrose or starch (1b).
- The consumption of large amounts of fructose seems to have an unfavourable effect on plasma lipoproteins (1b).
- The use of polyols as sweeteners does not seem to entail any risk (3b).

### 4.1.6 Starch
Starch in its indigestible form primarily comes from vegetables and cereals. Several studies have shown that blood glucose increases less after a meal with a high content of indigestible starch than after a meal with a high content of digestible starch. Long-term studies have yielded differing results regarding the effect on glycaemic regulation, however (116-119) (1b) (120) (3b). It is unclear whether the consumption of digestible starch better protects against nocturnal hypoglycaemia in insulin-treated Type 2 diabetes patients than other carbohydrates.

**Subconclusion**
- There is no advantage associated with the inclusion of large amounts of indigestible starch in the diet in Type 2 diabetes (1b).

### 4.1.7 Artificial sweeteners
As regards sweeteners such as saccharin and aspartame, the same rules apply as for persons without Type 2 diabetes. It is unclear whether the use of these sweeteners has an effect on glycaemic regulation or body weight, e.g. by stimulating the appetite. A controlled study of persons without Type 2 diabetes showed that the consumption of light soft drinks leads to a smaller weight gain than the consumption of non-light products of the same drink (103) (1b).
4.1.8 Protein

Protein intake is recommended to comprise approx. 20% of the daily energy intake. It is recommended to consume approx. 1 g/kg of body weight/24 hours. A few pathophysiological studies indicate that badly regulated Type 2 diabetes patients have an enhanced protein metabolism and hence an increased need for protein (121-123 (1b) (124) (3b).

It has been suspected that enhanced protein intake disposes to diabetic nephropathy (125) (2c). No studies exist that confirm this assumption with regard to Type 2 diabetes (126, 127) (1b) (128, 129) (2b) (130) (2c) (131) (3b) (132) (4). Several studies have shown that an enhanced intake of protein does not affect glycaemic regulation (133, 134) (1b) (135) (3b). It has been a matter of discussion whether a high protein intake promotes weight loss. In a study running over 12 weeks, weight loss was greater but LDL cholesterol was enhanced in the group on high protein and low carbohydrate intake (such a diet also contains more fat) (136) (3b). In another study, 54 overweight Type 2 diabetes patients were randomised to a diet with a high protein content (28%) or to a diet with a low protein content (16%) for 12 weeks. For the first eight weeks the diet was hypocaloric (1,600 kcal/day), while the last four weeks it was isocaloric (137) (1b). Surprisingly, the women lost more weight on the high-protein diet, while there was no difference in weight loss between the two groups in men. No differences in glycaemic regulation were found between the groups. The reduction in LDL cholesterol was most pronounced in the high-protein group. No long-term studies exist indicating that a diet with a high protein content leads to enhanced satiety or reduces the appetite with a resultant weight loss (138-140) (1b) (141-143) (3b).

Subconclusion

- Intake of protein does not increase the plasma glucose concentration in Type 2 diabetes (1b).
- The protein requirement is fully met by the recommended normal intake, even in the case of Type 2 diabetes patients whose glycaemic regulation is sub-optimal (3b).
- A diet with a high protein content and a low carbohydrate content does not promote weight loss and does not improve glycaemic regulation in the long term (1b).
- A high intake of protein (>20% of the total daily calorie intake) over a long period in patients without albumin excretion in the urine does not contribute to the development of diabetic nephropathy (2b).

4.1.9 Fat

Patients with Type 2 diabetes have a considerable excessive mortality from cardiovascular diseases. The fat intake is of considerable significance for the cholesterol concentration in the blood. It is therefore important to focus on the treatment of the diabetic dyslipidaemia by optimising the fat content in the diet. The primary goal for the dietary change in relation to the fat content of the diet is to reduce the intake of saturated fat and cholesterol (144, 145) (1a) (146) (3b). The background for recommending a diet with a low content of saturated fat and cholesterol in Type 2 diabetes is illustrated by a meta-analysis of 37 dietary studies (147) (1a). This showed that the recommended diet lowered total cholesterol by 10%, LDL cholesterol by 12% and triglycerides by 10%, while HDL cholesterol remained unchanged. A diet with an even lower content of saturated fat (<7%) and cholesterol led to a 16% fall in LDL cholesterol, but also to a 7% fall in HDL cholesterol. If dietary change is combined with increased exercise, an even greater fall in the lipids is observed, while the fall in HDL cholesterol is counteracted. The above-mentioned meta-analysis only encompasses studies that do not include Type 2 diabetes patients. Long-term studies of Type 2 diabetes patients do not exist. Recommendations for Type 2 diabetes patients do not differ from the general recommendation that saturated fat should be reduced to 10% of the energy intake and cholesterol to 300 mg/day. This will entail a high intake of carbohydrates, however, corresponding to 50-55% of the caloric intake. Glycaemic regulation is not affected when saturated fat is substituted by carbohydrates (148-150) (1b) (151) (3b) (152, 153) (4).

Diets with a high content of monounsaturated fat have been found to improve glycaemic regulation and the lipid status compared with a diet with a high content of saturated fat (147) (1a) (148, 149, 154) (1b) (151) (3b) (152, 153, 155) (4). Monounsaturated fat also seems to reduce insulin resistance (156) (1b). Increased intake of monounsaturated fat has been found to be associated with a low daytime blood pressure (157) (1b). Saturated fat can therefore be substituted by either carbohydrate or monounsaturated fat. Both dietary components also contribute to a reduction in plasma LDL cholesterol (158) (1b). An inconvenience is that a high intake of monounsaturated fat can lead to increased calorie intake and weight gain (147) (1a), and that a high content of carbohydrate can lead to increased levels of triglycerides (158) (1b). The influence of polyunsaturated fat on blood lipids and glycaemic regulation is only poorly investigated (159, 160) (1b). The dietary ratio of carbohydrates to monounsaturated fat will largely depend on the dietary habits of the patient.
Omega-3 fatty acids mainly derive from oily fish and from plant sources. Omega-3 fatty acids have been found to reduce raised triglycerides (161) (3b) and to have a favourable effect on the blood platelets and the thrombogenesis so that there is less tendency to form blood clots (162) (1b). In Type 2 diabetes patients a minor increase in HDL cholesterol and a fall in triglyceride concentration have been found upon intake of omega-3 fatty acids (163) (1a) (164, 165) (1b) (166, 167) (4). Omega-3 fatty acids normally seem to have a neutral effect on glycaemic regulation (168, 169) (1a) (170) (4). Moreover, omega-3 fatty acids have been found to be able to reduce sudden death by approx. 20% in patients with cardiovascular diseases (171) (1a) (172, 173) (1b) (174-176) (2b). In GISSI Prevenzione, 11,324 persons with a history of cardiac infarct were included, of which 1,683 had diabetes, (171) (1a). The treatment consisting of 1g of omega-3 fatty acids per day (corresponding to approx. 100 g of oily fish) reduced mortality, non-fatal cardiac infarct and apoplexy by 10% over 3.5 years, total mortality by 20% and cardiovascular mortality by 30%. Sudden unexpected death in particular was reduced in the group treated with omega-3 fatty acids.

As regards the intake of trans fatty acids, which among other things are found in margarines, the same rules apply as to the population in general, and reference is here made to either the Danish Nutrition Council report or a recent review of Stender and Dyerberg (178) (4). There are no studies in which Type 2 diabetes patients are included. It is primarily the promoting effect of the trans fatty acids on ischaemic heart disease that has caused the Danish Nutrition Council to recommend cessation of the use of industrially manufactured trans fatty acids (recommended maximum daily intake <2 g). Population groups consuming large amounts of chips, microwave popcorn, chocolate bars, fast-food and the such like are at increased risk of consuming too much trans fatty acids. The pathophysiology behind the increased risk of cardiovascular disease has not been elucidated, but trans fatty acids change the ratio between LDL cholesterol and HDL cholesterol in an undesirable direction. Triglyceride levels are also positively associated to the trans fatty acid intake.

Plant stanols/sterols are discussed in the Section “Treatment of dyslipidaemia in dietary change”.

Low-fat diets are most often used to promote weight loss, especially in combination with enhanced physical exercise (147) (1a) (179) (1b) (180) (3b) (181, 182) (4). Studies using ad libitum energy intake of a diet with a low fat and a high carbohydrate content have been found to promote weight loss compared to the normal hypocaloric diet, which is mainly used in the treatment of overweight and diabetes in Denmark (183-188) (1b) (189, 190) (2b) (151) (3b) (191, 192) (4). Weight loss has been associated with a fall in total cholesterol, triglyceride and an increase in HDL cholesterol. Low-fat diets have also turned out to better maintain a weight loss than other types of low-energy diets (147, 193) (1a) (179, 194-196) (1b).

The use of artificial fats such as Olestra, has not been introduced in Denmark, and there are no long-term studies on effects and side effects.

As to the question of whether dietary compositions exist that are especially suited to prevent cardiovascular diseases lies outside the scope of the present HTA report, and reference is here made to a recent review of this issue (197).

Subconclusion

- Saturated fat should constitute less than 10% of the energy intake (1a).
- Daily cholesterol intake should be less than 300 mg (1a).
- Consumption of trans fatty acids should be minimised (1b).
- Consumption of fat should be limited if weight loss and reduction in LDL cholesterol are desired (1a).
- If weight loss is not desired, the saturated fat can be replaced by carbohydrate or monounsaturated fat (1b).
- In weight-neutral diets, monounsaturated fat can substitute carbohydrate with a favourable effect on postprandial hyperglycaemia and plasma triglycerides, but not necessarily on HbA1c (4).
- Low-fat diets can contribute to weight loss (1b).
- Consumption of fish several times per week can be recommended (4).

4.1.10 Vitamins and minerals

Rules for the intake of vitamins follow the common guidelines for the population in general. In relation to antioxidants there are no studies indicating that it should be particularly favourable for Type 2 diabetes
patients to consume increased amounts of antioxidants (198) (3b). The background for the interest in antioxidants is the increased oxidative stress that hyperglycaemia induces in the body, among other things increased oxidation of LDL particles, which enhances their absorption and accumulation in the body (199) (1a) (200) (4). Vitamin E is an antioxidant in relation to LDL particles. Beta-carotene can also act as an antioxidant and is found together with vitamin E in the LDL particle. Vitamin C also works as an antioxidant of LDL particles by re-forming oxidised vitamin E. Several epidemiological studies have shown an inverse correlation between these vitamins and the occurrence of cardiovascular diseases (see among others (201) (1b) for a review of the literature). In the Heart Protection Study, which encompassed 25,000 persons, including 6,000 patients with diabetes, no effect was found on mortality and cardiovascular disease after five years with increased intake of 20 mg beta-carotene, 250 mg vitamin C and 600 mg vitamin E (201) (1b). The HOPE study included 9,541 persons, of which 38% had diabetes (202) (1b). Supplementary vitamin E (400 units/day) for 4 1/2 years did not result in any reduction in morbidity and mortality. In GISSL Prevenzione the administration of 300 mg supplementary vitamin E to patients with a history of cardiac infarct (including 1,683 persons with diabetes mellitus) had no effect on mortality and the occurrence of cardiovascular disease after 3.5 years of treatment (171) (1b). The above-mentioned negative results are in line with the results of large studies such as the ARED study (n=4,500) which used 400 units of vitamin E, 500 mg vitamin C and 15 mg beta-carotene (203) (1b), the Primary Prevention Project (n=4,500) (204) (1b), where the supplement consisted of 300 mg vitamin E, and the Alpha-Tocopherol Beta-Carotene (ATBC) study (n=29,000), which used 50 mg vitamin E or 20 mg beta-carotene daily (205) (1b). Other studies have used 15 or 30 mg beta-carotene alone or in combination with vitamin E or vitamin A, without this having any effect on morbidity and mortality (206-208) (1b). In the 12-year-long Physicians’ Health Study, where 25,000 persons were randomised to beta-carotene, the results were also negative (207) (1b). Increased intake of antioxidants can cause diarrhoea, haemorrhage and toxic reactions (209) (1a).

In studies with beta-carotene there was a surprising increase in lung cancer in the beta-carotene group (210, 211) (1b).

The effect of the B vitamins B1, B6 and B12 in the treatment of diabetic neuropathy has never been documented (212, 213) (1a).

In a randomised, placebo-controlled study from general practice in North Carolina, USA, in which Type 2 diabetes patients received an ordinary multivitamin pill combined with mineral supplement for a year, the occurrence of infections decreased (214). Thus 93% of the placebo group reported an infection compared with 17% in the group receiving the supplement. The infections mainly consisted of upper respiratory tract infections and influenza-like symptoms. The study also indicated that Type 2 diabetes patients could suffer from a lack of vitamins. The former group was also more frequently absent from work. The study comprised only a few Type 2 diabetes patients, and a larger study is necessary in order to confirm the results.

The idea has been aired that the minerals calcium, magnesium and perhaps zinc and chromium are associated with decreased carbohydrate tolerance. Two American studies (215, 216) (1b) and two Finnish studies (217) (1b) (218) (4) have not been able to find any effect of chromium on glucose tolerance. As regards zinc, minor studies of elderly individuals with Type 2 diabetes indicate that zinc could promote wound healing (212, 213) (1a). The daily intake of 1,000-1,500 mg calcium is recommended for elderly people with diabetes. It is also of importance as regards the occurrence of osteoporosis. Magnesium is important for the secretion of parathyroid hormone, and in epidemiological studies, a lack of magnesium in Type 1 diabetes patients has been associated with the degree of retinopathy (219) (4). No long-term studies of the value of magnesium supplement in Type 2 diabetes exist.

Subconclusion

- The intake of antioxidants over and above what is normally present in the diet does not have any beneficial effect (1b).
- Calcium supplement can reduce the occurrence of osteoporosis in women (4).

4.1.11 Alcohol and Type 2 diabetes

The same rules for alcohol consumption apply as for the population in general. Epidemiological studies including Type 2 diabetes patients have shown that the daily intake of 1-2 drinks has a protective effect towards cardiovascular diseases (220-222) (2b). In relation to the diabetes patient, one should pay special attention to reducing the intake of alcohol in patients with pancreatitis, peripheral neuropathy or increased triglycerides. Alcohol intake can be associated with both hyperglycaemia and hypoglycaemia in sulphonyl
Non-pharmacological treatment of hypertension in Type 2 diabetes has primarily focussed on weight reduction (246-248) (3b). The consumption of even minor amounts of alcohol can change or reduce the symptoms of hypoglycaemia (229) (1b). Alcohol can delay contra-regulation after hypoglycaemia as it inhibits hepatic glyconeogenesis (glucose production) (228) (4). The consumption of moderate amounts of alcohol (up to 21-28 g daily) does not have any influence on the blood glucose concentration (230-233) (1b) (234, 235) (2b) (223-225, 236-238) (3b) (239) (4). The risk of hypoglycaemia in Type 2 diabetes after alcohol intake is only increased in the case of insulin treatment or treatment with drugs that stimulate insulin secretion. There seem to be a relationship between alcohol intake and blood pressure. The consumption of moderate amounts of alcohol does not raise blood pressure (240) (1a) (241) (3b), whereas chronically high consumption (over 30 g per day) can raise blood pressure (242) (1a). Alcohol stimulates the secretion of VLDL cholesterol and increases triglyceride in the blood (243) (2b) (244) (3b).

Epidemiological studies, among others the large American “Nurses' Health Study”, have shown that the daily intake of 1-2 drinks can protect against Type 2 diabetes (234, 235, 245) (2b).

**Subconclusion**

- Persons suffering from pancreatitis, peripheral neuropathy and markedly increased triglycerides should not consume alcohol (5).
- Intake of moderate amounts of alcohol with the food does not affect the blood glucose concentration (1b).
- Intake of small amounts of alcohol does not raise the blood pressure, in contrast to intake of larger amounts of alcohol (1a).
- Intake of moderate amounts of alcohol reduces the risk of developing Type 2 diabetes, cardiac disease and stroke (2b).
- Patients undergoing treatment with sulphonylurea or insulin should be aware of hypoglycaemia when consuming alcohol (5).

**4.1.12 Treatment of hypertension through dietary change**

Non-pharmacological treatment of hypertension in Type 2 diabetes has primarily focussed on weight reduction (246-248) (1b) and reduced sodium intake (249) (1b) (250, 251) (2a). Other dietary components able to influence the blood pressure are alcohol (252) (4), potassium (253) (1a) (249) (1b) and calcium (254) (1a) (255) (2b) (256) (3b). Few of these studies included diabetes patients. Several meta-analyses have shown a relationship between the magnitude of sodium intake and blood pressure (257-259) (1a). In a meta-analysis of 32 studies that together encompass 2,635 persons, a reduction in sodium intake led to a 5 mmHg fall in systolic pressure and a 2-3 mmHg fall in diastolic pressure in hypertensive persons, although with considerable variation in the results (257) (1a). Another meta-analysis of 56 studies (258) (1a) found a 4 mmHg fall in systolic pressure and 1 mmHg fall in diastolic pressure with a 100 mmol reduction in sodium intake. The DASH study (260) (1b(F)) compared three diets: 1) a traditional American diet, 2) a diet with a high content of fruit and vegetables, and 3) the DASH diet, which contained a high proportion of fruit and vegetables and a low fat content (261, 262) (1b) (260) (1b(F)) (263) (4). Compared with the traditional diet the other two diets resulted in lower systolic and diastolic blood pressure over an 8-week period. The DASH diet reduced the blood pressure by 6 mmHg and 3 mmHg compared with the control diet (261, 262) (1b) (260) (1b(F)) (263) (4). In the groups on the traditional diet and the DASH diet, a low salt intake (50 mmol sodium/day) compared to a high salt intake (150 mmol sodium/day) resulted in a 6-7 mmHg fall in systolic pressure and a 2-3 mmHg fall in diastolic pressure (261, 262) (1b) (260) (1b(F)) (263) (4). In a recent meta-analysis of randomised studies focussing on lifestyle intervention in the form of salt restriction in patients with hypertension, and with a duration ranging from six months to seven years (median 36 months), no difference in mortality was found between the group that was given lifestyle intervention and the control group. The systolic blood pressure was 1.1 mmHg lower and the diastolic pressure 0.6 mmHg lower in the intervention group (264) (1a). It thus seems that lifestyle programmes with dietary changes, which can be difficult to implement in general practice or to use in a national strategy, only lead to minor falls in blood pressure. In epidemiological studies the effect of low sodium intake has varied, with the occurrence of cardiovascular disease being reportedly both higher and lower (265-268) (2b).

A meta-analysis of 11 “weight loss studies” showed that systolic and diastolic blood pressure both decreased by 1 mmHg per kg weight loss (269) (1a). In the Swedish SOS study it was found that the great average weight loss of 28 kg in the operated group led to an initial significant fall in blood pressure, but that no difference in blood pressure was detectable at the 6-8-year follow-up despite a weight difference of 20-22 kg between the control group and the operated group (270) (2a).
The consumption of more than three drinks per day has been found to be associated with an increased risk of raised blood pressure (271, 272) (1b). In controlled studies, potassium supplement has been shown to reduce blood pressure (273) (1a) (252) (4), but there is no evidence that calcium and magnesium supplement affects blood pressure (273) (1a).

Subconclusion

- The consumption of 1-2 drinks per day does not have any effect on blood pressure (1b).
- A low-fat diet that includes fruit and vegetables reduces blood pressure (1b).
- The consumption of more than three drinks per day has been found to be associated with an increased risk of raised blood pressure (271, 272) (1b).

4.1.13 Treatment of dyslipidaemia through dietary change

Diabetic dyslipidaemia is characterised by high triglycerides, low HDL cholesterol and an increased occurrence of “small, dense” LDL particles. The latter are particularly atherogenic. The pathophysiological background for this combined dyslipidaemia is the insulin resistance. With treatment of the dyslipidaemia in Type 2 diabetes the primary focus is on LDL cholesterol, while HDL cholesterol and triglycerides come second. Treatment always starts with lifestyle changes. A diet is recommended with <10% saturated fat and a cholesterol intake of <300 mg per day. Moreover, glycaemic regulation should be optimised. The effect of good glycaemic regulation is primarily reflected in the triglycerides, which fall. In overweight patients, weight loss and enhanced exercise are recommended as these effectively increase HDL cholesterol and decrease triglycerides (274-276) (1a) (277) (2b) (278) (3b) (279) (4), among other things by enhancing insulin sensitivity (280) (1b). If the therapeutic goals have not been achieved after three months with lifestyle changes, pharmacotherapy should be considered. In Type 2 diabetes patients with lightly to moderately raised plasma triglycerides and a low HDL cholesterol concentration the substitution of saturated fat with carbohydrate (148, 149) (1b) (281-283) (3b) (284) (4) seems to result in an increase in HDL cholesterol and a neutral or beneficial effect on plasma triglycerides, though not in all studies (285, 286) (1b). Saturated fat can be substituted with monounsaturated fat (156-158, 287) (1b), though with a risk of weight gain. Plant stanols/sterols are able to lower total cholesterol by up to 10-14% and LDL cholesterol by 15-20% (288-290) (1b), primarily by inhibiting cholesterol uptake from the gut. However, it is necessary to consume larger amounts than normally taken in with the diet in the form of margarine, oils etc. Stanols, which are used to enrich foods, are a by-product of industrial paper production (291) (1a). There are no controlled clinical studies showing that stanols have any effect on cardiovascular disease (291) (1a). Among other things, sterols and stanols also inhibit the absorption of fat-soluble vitamins and other nutrients. The substances accumulate in a number of tissues, e.g. the adrenal glands and ovaries, but the significance of this is unclear.

With dietary change a maximal decrease in LDL cholesterol of approx. 0.7 mmol/l or 10-15% of the starting value can be expected (292, 293) (1b) (294) (1b(F)). Thus if LDL cholesterol is more than 0.7 mmol/l above the therapeutic goal, pharmacotherapy is often necessary (293) (1b) (294) (1b(F)).

Omega-3 fatty acids lower triglycerides in patients with Type 2 diabetes (168, 169) (1a), but can increase LDL cholesterol, perhaps due to a shift to fewer “small, dense” LDL particles (168, 169) (1a). For patients with plasma triglycerides above 10 mmol/l and the risk of developing pancreatitis, arthritis and fatty infiltration of the liver, treatment with low-fat diets is recommended, possibly in combination with a fibrate (295, 296) (1a).

The latest American guidelines for treatment of diabetic dyslipidaemia suggest that in patients with raised LDL cholesterol (>3.6 mmol/l), lifestyle changes and pharmacotherapy should be initiated concomitantly (297) (1a).

Subconclusion

- Type 2 diabetes patients with raised LDL cholesterol should reduce the intake of saturated fat to less than 10%, possibly to less than 7% (5).
- Saturated fat can be replaced with carbohydrates or monounsaturated fat (1b).
- In Type 2 diabetes patients with raised triglycerides, reduced HDL cholesterol and increased levels of small, dense LDL particles, a moderate weight loss, reduced intake of saturated fat and increased physical activity will have a beneficial effect on dyslipidaemia (1b).
Good glycaemic regulation per se has only moderate effect on diabetic dyslipidaemia (1b).

The LDL cholesterol level can be reduced by increasing the intake of water soluble fibre (1a).

Persons with raised triglycerides exceeding 10 mmol/l should primarily be treated with low-fat diet, possibly in combination with fibrates (1a). The most effective part of the treatment is to reduce the intake of fat, but not of omega-3 fatty acids (2b).

4.1.14 Nephropathy

Once diabetic nephropathy has developed, its progression can result in the need for dialysis or kidney transplantation. In order to prevent this progression the patients are treated with aggressive blood pressure control and good glycaemic regulation. The significance of protein restriction for progression of nephropathy has been a matter of discussion. In four studies it has been shown that in patients with microalbuminuria, the forerunner for diabetic nephropathy, protein restriction improves renal function. In another three studies it reduced the urine albumin level (111, 298-300) (1b). In Type 1 diabetes, reduced protein intake is associated with a reduced fall in GFR (glomerular filtration rate) in follow-up periods of up to three years (301, 302) (1b). It is unclear whether specific types of protein (plant versus animal protein) have a particularly favourable effect on diabetic nephropathy.

Subconclusion

A reduction in daily protein intake to 0.8-1 g/kg/day in persons with microalbuminuria and to 0.8 g/kg/day in Type 2 diabetes patients with diabetic nephropathy delay the progression of diabetic nephropathy (1b).

No data are available that lead to the recommendation of special forms of protein (5).

4.1.15 Treatment of overweight in Type 2 diabetes

Patients with Type 2 diabetes are often overweight (80-90%) with an increased fat mass, which induces increased insulin resistance. It is also a problem that treatment with sulphonylurea, insulin, glitazones, etc. entails a further weight gain and therefore often fails to improve glycaemic regulation in the long term. The weight increase during insulin treatment can be reduced by combining insulin with metformin and administering insulin as night insulin at bedtime (303) (1a). Clinical studies have shown that a 2.5 percentage point improvement in HbA1c or an approx. 5 mmol/l fall in fasting blood glucose results in an average weight gain of 5 kg over the first year after starting insulin treatment. This weight gain can be approximately halved by combination treatment with metformin and insulin. Obesity also worsens the diabetic dyslipidaemia and is associated with hypertension (304) (1a) (305) (1b) (306) (2b) (307) (3b).

Weight loss is therefore the most rational treatment of Type 2 diabetes. Studies of up to six months duration have shown that weight loss enhances insulin sensitivity and reduces hepatic glucose production, thereby improving glycaemic regulation, diabetic dyslipidaemia and blood pressure (274) (1a) (308) (3b) (279, 309, 310) (4). The background for the poor treatment results in weight loss attempts is illustrated by the fact that only approx. 6% of the patients can be expected to maintain a weight loss of 5% for more than 9-15 years (311) (2b).

The most important component in the treatment of overweight is probably dietary change with the intake of a low-fat, hypocaloric diet (183, 184) (1b). In accordance with this, epidemiological studies have shown a relationship between the fat content of the diet and the occurrence of obesity (312) (1b) (313) (4). Toubro and Astrup (196) (1b) compared the effect of an ad libitum diet with a low fat content and a high carbohydrate content with a fixed energy intake diet. At the 1-year follow-up the ad libitum group showed the greatest weight loss. No randomised long-term studies evaluating the effect of lifestyle changes exist for Type 2 diabetes.

As discussed later, exercise increases insulin sensitivity and can acutely reduce blood glucose in patients with Type 2 diabetes (314) (4). Exercise per se has only a moderate effect on weight (315) (1a). On the other hand, exercise seems to be of great importance for maintaining a weight loss (274) (1a) (316) (1b). As discussed below, the most important component of a weight loss programme seems to be the number of outpatient check-ups, however.

It is vital to establish realistic goals for the weight loss, which for most people will be approx. 5-10 kg. For many people, simply stabilising their weight would be considered a success.

In the following, key studies showing that dietary change can be implemented and can improve metabolic
regulation are discussed. In relation to Type 2 diabetes the most successful study (317) (2b) led to a weight loss of 9 kg over a 6-year period. In the newly published Diabetes Prevention Program (DPP) (318) (1b), which included approx. 3,000 persons with impaired glucose tolerance, a weight loss of 7% was obtained the first year and an average weight loss of approx. 5% in the 3-year follow-up period. The persons underwent an intensive programme consisting of dietary change and increased exercise. The patients were motivated through 16 consultations in the first 24 weeks and thereafter one consultation once per month. Wing et al. (319) (1b) demonstrated a 2.5 kg weight loss, and a Finnish study found an average weight loss of 3.5 kg over two years through similar intensive programmes (320) (1b). In the UKPDS, 2,595 newly diagnosed patients were treated with lifestyle changes during the first three months (321) (1b), which entailed a 1.9 percentage point fall in HbA1c. The average weight loss was 5 kg after three months. The UKPDS is the key study within Type 2 diabetes. The significance of weight loss for glycaemic regulation in the UKPDS will therefore be examined in detail.

At the time of diagnosis, the patients in the UKPDS were recommended a diet consisting of 50% carbohydrate, 30% fat and 20% protein with an energy restriction that was tailor-made for the patient's weight and level of activity (321). On average the patients consumed 1,361 kcal/day. The patients were seen in an outpatient clinic once a month during the first three months after diagnosis. Fifteen percent of the included patients could not maintain a fasting blood glucose of under 15 mmol/l during the first three months. Characteristically for this group of patients, they had higher fasting glucose at the time of diagnosis and that a relatively greater percentage were of standard weight. Among the remaining 2,597 patients average overweight fell from 130% to 123% of the ideal weight, i.e. an average weight loss of 7% over three months. The weight loss was associated with a fall in fasting glucose from 11.4 to 8.1 mmol/l. The centres with access to the best dietary guidance also achieved the greatest weight losses and the greatest falls in blood glucose. In 18% of the patients in the UKPDS the fasting glucose was normal after three months. The weight loss in this group of patients averaged 11%. Approximately 50% of the patients who started with a fasting blood glucose of 6.0-8.0 mmol/l had a normal fasting blood glucose after three months. In comparison, only 10% of the group who had an initial blood glucose of 16-22 mmol/l were able to achieve a normal blood glucose through dietary change. Fifty-four percent of the patients who had a normal fasting blood glucose after three months had a normal blood glucose after 15 months, at which time they had lost a further 3%. The 46%, who were unable to maintain normal fasting blood glucose after 15 months had gained 2% in weight. After three years only approx. 23% were able to maintain a HbA1c under 7.0% on dietary treatment alone, while the percentage had fallen to 11% after nine years (322) (1b). These data show the Type 2 diabetes is a progressive disease such that within a few years of diagnosis, pharmacotherapy is needed to maintain a glycaemic regulation with HbA1c <7.0%.

In a study over two years, Blonk and co-workers (323) (1b) found that the group treated with dietary intervention and enhanced physical activity initially had lost 2.9 kg as compared to 1.2 kg in the conventionally treated group, but that there was no difference between the groups after two years. In a randomised study encompassing 179 Type 2 diabetes patients where a visit to the clinical dietician was compared with a more intensive course of treatment that included at least three visits at the clinical dietician (324) (1b), HbA1c fell 1-2 percentage points in the intensively treated group and was greatest in the group with diabetes of the shortest duration. After six weeks to three months it was possible to decide whether the therapeutic goal could be obtained through lifestyle changes. In concert with this, Kulkarni and co-workers found the greatest effect in the intensively treated group (325) (1b). A cross-over study from Glasgow and co-workers (326) (1b) showed that HbA1c decreased most in the intensively treated group, but that this effect disappeared after the cross-over, when HbA1c in the former conventionally treated group decreased from 7.4 to 6.4%. Sadur and co-workers showed that frequent controls at a diabetes team led to a 1.3 percentage point fall in HbA1c as compared with 0.3 percentage points in the conventionally treated group (327) (1b). These studies show the significance of including a clinical dietician in the diabetes team and of frequent consultations. In line with this, a retrospective study has compared 81 patients who had had three consultations with a clinical dietician with 81 patients who had never consulted a clinical dietician (328) (1b). In the former group, HbA1c fell by 2.1 percentage points as compared with 0.2 percentage points in the latter group. In a meta-analysis of 89 studies (329) (1a), dietary change was found to have no effect on weight and metabolic regulation. Other lifestyle changes only had a marginal effect. In the meta-analysis by Norris and co-workers (330) (1a) of 72 randomised studies, an effect of lifestyle changes was detected during the first six months. In more long-term studies no evidence was found that attempts at lifestyle change were effective. Education was effective as regards enhancing knowledge about diabetes and learning practical abilities such as self-monitoring of glucose. No studies have demonstrated a reduction in cardiovascular events in Type 2 diabetes patients through lifestyle changes.
Lifestyle changes that lead to weight loss are therefore difficult to implement. Few Danish results from general practice and diabetes outpatient clinics concerning the changing of lifestyle habits in Type 2 diabetes patients are available. Two studies exist where lifestyle changes have been attempted. One of the studies is from general practice (331) (1b). A total of 311 practices with 474 physicians were randomised to structured, individualised treatment or routine treatment of Type 2 diabetes. A total of 874 patients were followed for six years. The structured treatment consisted of the establishment of individual treatment goals supported by written reminders, clinical guidelines, patient status reports and courses for the physicians. At the 6-year follow-up the occurrence of late diabetic complications and mortality did not differ in the two groups. HbA1c, cholesterol and systolic and diastolic blood pressure were lower in the group for whom individual goals had been set. After six years the groups had achieved a weight loss of 2.0 and 2.6 kg, respectively, from the time of diagnosis. It did not prove possible to change smoking or exercise habits in either of the groups, just as there were no differences in the diet after six years. Twenty-five to thirty percent of the patients measured urine or blood glucose at home in 1995 after six years. Intervention thus had little effect on the lifestyle. In the Steno 2 study (332) (1b), 80 patients with microalbuminuria were followed in general practice, while 80 patients were randomised for intensive treatment at the Steno Diabetes Center by a diabetes team that also included a clinical dietician. At the 4-year follow-up the former group had gained 0.5 kg in weight as compared with 3.7 kg in the latter group. After eight years the weight gain was 2 kg versus 2.6 in the intensively treated group. The number of smokers had fallen from 29 to 22%, and the amount of exercise had increased from 3.7 kg in the latter group. After eight years the weight gain was 2 kg versus 2.6 in the intensively treated group. The number of smokers had fallen from 29 to 22%, and the amount of exercise had increased from 163 to 215 min per week in the intensively treated group (333, 334) (1b). The study also showed that it requires great resources to change lifestyle, and that weight loss in particular is difficult to obtain in middle-aged Type 2 diabetes patients with longer-lasting diabetes that is intensively treated, often with insulin. The above-mentioned studies also illustrate that the effect of lifestyle changes seem to be short lasting. Specific problems concerning weight loss in Type 2 diabetes will be discussed below.

Subconclusion

- Several visits to a clinical dietician can result in weight loss and a fall in HbA1c of approx. 2 percentage points in newly diagnosed patients, and up to 1 percentage point in patients with longer duration diabetes of approx. 4 years (1b).
- A reduced calorie intake, primarily in the form of a reduction in fat intake seems to be able to evoke a weight loss of 3-10 kg the first year (1b).
- The majority of the patients will begin to gain weight again 4-6 months after the start of dietary change, and the majority will weigh the same or more than the starting weight after 2-4 years (1b).
- Regular exercise seems to be important for maintaining a weight loss (1a).
- Dietary change can be effective as monotherapy at the time of diagnosis (1b).
- Attempts at lifestyle change, including dietary change, have poor or no effect on weight 6-12 months after discontinuation of the intervention (1a).

4.1.16 The use of VLCD diets (very low calorie diets)

VLCD diets contain approx. 800 calories/day and, if followed, entails a weight loss of approx. 10% or 10-15 kg in the course of 8-12 weeks (335) (4). However, a large part of the weight loss has been regained 1-2 years after the start of the treatment (336-338) (1a) (339) (1b), although this can partly be hindered by combining VLCD with other lifestyle changes (339-341) (1b). If VLCD diets are used by Type 2 diabetes patients treated with sulphonylurea or insulin, special precautions have to be taken to avoid hypoglycaemia.

VLCD leads to a very rapid improvement in glycaemic regulation (days) and in dyslipidaemia in Type 2 diabetes patients, especially of the triglycerides (340) (1b) (308) (3b). One study has shown that it is the calorie restriction that is largely responsible for correcting the hyperglycaemia. The improved glycaemic regulation is detected before a significant weight loss. Discontinuation of VLCD and the initiation of a normal diet thus leads to a day-to-day deterioration in glycaemic regulation (342, 343) (1a).

In two studies (340, 344) (1b) where lifestyle changes were combined with VLCD, a weight loss of up to 13-14 kg was achieved after six months and an average weight loss of 10.5 kg after 1-2 years. Blood glucose fell an average of 3.4 mmol/l and HbA1c fell 1.7 percentage points, despite the fact that the doses of oral antidiabetics and insulin were reduced. In another study (340), the Type 2 diabetes patients in the VLCD group achieved an initial weight loss almost twice that of the group treated with a hypocaloric diet of 1,000-1,500 kcal. At the 1-year follow-up there was no difference between the two groups as regards the magnitude of the weight loss. However, the group treated with VLCD achieved a greater fall in HbA1c, and this was still the case after one year (9.2% versus 11.8%). One study (344) (1b) included two periods of VLCD of 12 weeks duration (weeks 1-12 and 24-36) with weekly consultations to ensure implementation of lifestyle
changes. The control group was treated with a conventional hypocaloric diet. The VLCD group lost 16 kg during the first period on VLCD as compared with 11.1 kg in the control group. However, compliance during the second VLCD period was so poor that it only resulted in a weight loss of 1.4 kg. After 50 weeks, there was no difference in the magnitude of the weight losses in the two groups (340) (1b). In another design VLCD was used on one day per week or on five consecutive days every fifth week. In the course of 20 weeks the latter group had lost 10.4 kg, the 1-day group 9.6 kg and the control group 5.4 kg. Fasting glucose and HbA1c were significantly lower in the 5-day group (344) (1b).

Subconclusion

“Very low calorie diet” (VLCD) promotes an initial weight loss and improves glycaemic regulation. However, VLCD does not – even in combination with other lifestyle changes – seem to be able to maintain a long-term weight loss (1a).

4.1.17 Surgical treatment of obesity in Type 2 diabetes
Surgical modification of the gastrointestinal tract is effective with respect to provoking a weight loss (345-347) (4). The most common surgical procedures are “gastric banding”, which can be subdivided into “vertical gastric banding” and “adjustable gastric banding”, and “gastric by-pass”. In both types of procedure the upper part of the stomach is converted into a small volume of 25-30 ml. The new small gastric sac only allows the consumption of small meals. The consumption of large meals or major amounts of liquid causes pain and possibly vomiting. In a series of 70 obese patients treated with surgical transformation of the gastric sac (gastric banding), the weight loss was 37 kg after one year and 32 kg after three years (345) (4). In 515 obese persons weight losses of 50 and 45 kg were found after one and three years, respectively. At follow up after 7.6-years, 83% of 165 Type 2 diabetes patients had achieved remission of their Type 2 diabetes, and 99% of the persons with impaired glucose tolerance had achieved normal glucose tolerance (346) (4). 82% of the non-operated Type 2 diabetes patients needed antidiabetic medication versus 7.1% of the operated patient (346) (4). In another study of severely obese persons with Type 2 diabetes it was found that mortality was reduced 3-4-fold among those who underwent surgical treatment of obesity compared to those who were not operated (348) (3b). Ten years ago a major study of surgical treatment of obesity began in Sweden (349) (3b) with the primary aim of investigating the effect of weight loss on morbidity and mortality among severely obese persons (BMI >34 kg/m² for men and BMI >38 kg/m² for women). The investigation is planned to include 4,000 obese persons – half operated and half followed in general practice and treated with conventional treatment. After two years the operated group had lost 23% of the initial weight corresponding to 28 kg. At the 6-year follow-up the weight loss was 16-19% in the operated group compared with 1% in the control group (350). The greatest effect of weight loss was seen in the occurrence of Type 2 diabetes and in the improvement of the diabetes regulation in those who had diabetes at the start of the investigation (351). In relation to the development of diabetes, the effect of surgery increased the longer the observation time. After two years, the diabetic state had disappeared in 68% after surgery. Moreover, Type 2 diabetes developed in 0.2% after surgery compared with 6% in the control group (350). A marked improvement in blood pressure and lipoproteins, especially triglycerides, was also found, but at the 8-10-year follow-up there was no difference in blood pressure between the two groups. In a prospective study of 500 patients, 50 of whom had Type 2 diabetes, followed for one year after “gastric banding”, weight fell on average from 137 kg to 110 kg in patients with Type 2 diabetes, which was significantly less than the weight loss in persons without Type 2 diabetes who had been operated with the same method (347) (4). Maximal weight loss is not normally seen until 2-3 years after gastric surgery. After one year, 64% of the patients showed remission of their diabetes, and 26% had improved glycaemic regulation, while 10% had unchanged regulation. In all patients, HbA1c was <7%. Predictors of remission were the magnitude of the weight loss and short duration of diabetes (352) (1b). The operated persons achieved improved insulin sensitivity and beta-cell function. A significant improvement was also found in triglycerides (-43%), HDL cholesterol (+18%) and blood pressure (fell from 154/96 to 130/79 mmHg, and 15 patients no longer needed antihypertensive medication). The occurrence of sleep apnoea and depression was reduced, and quality of life was improved (almost 100%). Median hospitalisation time in this study was two days (347) (4). Pontiroli and co-workers followed 143 patients for three years after surgery that led to a fall in BMI from 45 to 37 kg/m² (353) (4). All persons with abnormal glucose tolerance achieved normal HbA1c and fasting blood glucose. The blood pressure also fell significantly.

The side effects of surgery are prolapse of the gastric ventricle through the band, which necessitating re-operation, and erosion of the band into the gastric ventricle, which necessitates removal of the band, possibly surgically. Other complications are peri- and postoperative mortality (approx 1%) and problems with wound healing, vitamin and mineral deficiency and gall stones (345-347, 354) (4). Long-term studies describing
morbidity, mortality, number of sick days and number of invalid pensions are lacking, but are underway from the Swedish SOS study (349) (3b). Presently, approx. 1,000 patients in each of the two groups have been followed for 10 years without the “Safety Commission” having found grounds to stop the study due to differences in mortality between the groups (350).

At present, surgical treatment of obesity is only performed at a few centres in Denmark, and the position of surgery (the indications) in the treatment of obesity is presently unclear in Denmark.

Randomised studies comparing pharmacological versus surgical treatment are not available.

Subconclusion
- Surgical treatment of extreme obesity results in considerable weight loss and often to remission of Type 2 diabetes and reduces the number of new cases of Type 2 diabetes (4).
- Surgical treatment results in a long-lasting weight loss of approx. 25% the first 1-2 years. After 10 years the weight loss is approx. 16%, corresponding to approx. 20 kg (2a).
- It is unclear whether surgical intervention should be recommended in Type 2 diabetes. Long-term data available comparing the advantages and disadvantages of surgical versus medical treatment are not available (5).

4.1.18 Is improvement in glycaemic regulation caused by weight loss or by calorie restriction?
The effect of dietary change on glycaemic regulation rapidly becomes apparent, most often within 7-10 days. In a study of 30 overweight Type 2 diabetes patients followed for 30 days on 330 kcal/day, 80% of the effect on glycaemic regulation was observed after 10 days (310) (4). Subsequently, as the calorie intake was increased, the glucose level increased despite the fact that the weight loss was maintained. These data show that the calorie intake is of greater significance for glycaemic regulation than weight (310) (4). In another study of overweight Type 2 diabetes patients treated with VLCD during the first two months after diagnosis and who lost 12.7 kg, 50% of the total reduction in fasting glucose occurred after only seven days (355) (3b). In a third study a group that lost 11% of their weight on VLCD (400 kcal/day), achieved a lower fasting glucose than Type 2 diabetes patients who had lost the same amount on 1,000 kcal/day (356) (1b). When the former group increased their calorie intake, the patients experienced a deterioration in glycaemic regulation despite the fact that their weight continued to decrease (356) (1b).

Subconclusion
- Both weight reduction and calorie restriction add to the effect of dietary change on glycaemic regulation. The rapid initial effect on glycaemic regulation shows the effect of calorie restriction (355) (3b).

4.1.19 What is the evidence that weight loss improves glycaemic regulation over a longer period?
The strongest evidence that weight loss over a longer period improves glycaemic regulation derives from surgical treatment of obesity, where the weight loss is greater than that which can be obtained through other treatment methods. In the SOS study, for which data is available for 767 persons who underwent surgery and 712 control persons followed for two years (357) (3b), the control group lost 0.5 kg on average compared with 28 kg in the operated group. Among persons who had diabetes at the time of randomisation, 69% experienced remission of their diabetes in the operated group as compared with 16% in the control group. In parallel with this, 2.7 times more persons experienced remission of hypertension, 1.9 times more achieved normal triglyceride levels, and 1.2 times more achieved normal cholesterol in the operated group (357) (3b).

In another study encompassing 146 persons with Type 2 diabetes (358) (2b) weighing 138 kg from the start, the weight was 87 kg one year after surgery, 93 kg after five years and 95 kg after 14 years. At the 14-year follow-up, 83% of the patients with diabetes (121 out of 146) had normal blood glucose and HbA1c. In this study the diabetes patients who had been treated surgically were compared with a control group in which had not been undertaken for various reasons. After nine years the percentage of patients needing pharmacotherapy for their diabetes had increased from 56% to 85% in the control group but had decreased from 31% to 8% in the operated group. Mortality was also found to be reduced in the operated group, 9% versus 28% in the control group.

4.1.20 How much weight has to be lost in order to improve glycaemic regulation?
Several studies have found a correlation between weight loss and the fall in HbA1c (359, 360) (1b) (323) (2b). Other studies, in which the patients were followed for two years and achieved a weight loss of up to 5.7 kg, have not been able to detect any improvement in HbA1c (344) (1b) (323) (2b). However, the
interpretation of these studies is always rendered difficult by the fact that the weight loss often entails a reduction in the pharmacotherapy, which might veil a favourable effect of weight loss on glycaemic regulation. The studies (361) (1a) (362, 363) (4) show that weight loss of 5-10% will probably lead to an improvement in glycaemic regulation over one year. In the UKPDS, patients who were 173% overweight on average and had a fasting blood glucose exceeding 15 mmol/l at the time of diagnosis had to lose equivalent to 36% of their ideal weight in weight in order to normalise the blood glucose value (Table 4.1.20.1). The group who were 121% overweight on average and had a fasting blood glucose of 6-8 mmol/l had to lose 16% of their ideal weight, corresponding to 10 kg. In the same patient group, but with fasting blood glucose exceeding 15 mmol/l, the weight loss needed was 43% of the ideal weight, corresponding to 26 kg, in order to achieve a normal blood glucose (Table 4.1.20.1).

**TABLE 4.1.20.1**
Weight loss (% of ideal body weight) necessary to achieve a fasting plasma glucose <6 mmol/l after three months of dietary change (UKPDS)

<table>
<thead>
<tr>
<th>Degree of obesity (weight excess)</th>
<th>Fasting plasma glucose (mmol/l) at time of diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6-8</td>
</tr>
<tr>
<td>&lt;110% of ideal weight (mean 102%)</td>
<td>ns</td>
</tr>
<tr>
<td>110-130% of ideal weight (mean 121%)</td>
<td>16%</td>
</tr>
<tr>
<td>130-150% of ideal weight (mean 139%)</td>
<td>14%</td>
</tr>
<tr>
<td>150% of ideal weight (mean 173%)</td>
<td>17%</td>
</tr>
<tr>
<td>All patients (mean 121%)</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>10 kg</td>
</tr>
</tbody>
</table>

**Subconclusion**
- The improvement in glycaemic regulation seems to be related to the magnitude of the weight loss. A weight loss of 5-10% of body weight improves glycaemic regulation (1a), but a weight loss of more than 20% is often required to normalise the fasting glucose concentration (1b).
- Large permanent weight losses can lead to long-term improvement in glycaemic regulation in Type 2 diabetes (2b).

**4.1.21 Which Type 2 diabetes patients improve their glycaemic regulation through weight loss?**
As the response to weight loss varies considerably, it is of interest to know the variables that determine whether weight loss leads to an improvement in regulation in the individual patient, i.e. for a given weight loss, which patients will exhibit the greatest improvement in glycaemic regulation? In relation to the duration of diabetes it seems that newly diagnosed persons respond more to weight loss than patients who have had diabetes for more than five years (364) (3b). Another study, however, finds the same effect of weight loss on glycaemic regulation irrespectively of the duration of diabetes (364) (3b). Patients with the highest fasting blood glucose at the time of diagnosis exhibit the greatest reduction in glucose concentration during weight loss (365) (1b) (363) (4). Moreover, it seems that the effect of a weight loss of 2.3 kg to 4.5 kg on glycaemic regulation after 2-3 months can be used to differentiate between patients who respond to a weight loss, and those who do not respond (127) (1b).

**Subconclusion**
The best predictors of the effect of weight loss on glycaemic regulation are the initial fasting blood glucose concentration and the glycaemic response to a minor weight loss after a few months treatment (127) (1b).

**4.1.22 Have persons with Type 2 diabetes more difficulty in losing weight than overweight persons without diabetes?**
In controlled studies, Type 2 diabetes patients typically lose less weight than persons without Type 2 diabetes. Moreover, they re-gain weight more rapidly and put on more (366-370) (1b). In randomised studies, average weight loss among Type 2 diabetes patients is half that of persons without Type 2 diabetes. In controlled studies with orlistat, diabetes patients always lost significantly less weight than persons without Type 2 diabetes, irrespective of whether they were treated with sulphonylurea, metformin or insulin. Moreover, while 2/3 of the persons without Type 2 diabetes lost more than 5% in weight, only half of the patients with Type 2 diabetes succeeded in doing so. Following gastric surgery with “gastric banding”, Type 2 diabetes patients also lose less weight than persons without Type 2 diabetes (347) (4).

**Subconclusion**
- It is more difficult for Type 2 diabetes patients to lose weight than for persons without Type 2 diabetes, and more research is needed to elucidate the mechanisms behind this (1b).
4.1.23 The effect of frequent outpatient controls on weight loss
In a study comparing weekly versus monthly outpatient contact (360) (1b), the patients with weekly outpatient contact lost an average of 6.9 kg over 16 weeks as compared with 2.9 kg in the group only treated with dietary change and monthly outpatient contact. The studies that have shown that Type 2 diabetes can be prevented have also clearly demonstrated the significance of frequent outpatient check-ups. In general, the effect of dietary change rapidly disappears if the outpatient check-ups cease. It is doubtful whether a single visit or two visits to a clinical dietician will result in a weight loss over a longer period. This issue will be discussed later in the section on education.

4.1.24 Which components of lifestyle changes have the greatest effect in relation to weight loss in Type 2 diabetes patients?
In a meta-analysis encompassing 89 short-duration (<6 months) studies, of which 40% concerned dietary intervention, 20% concerned lifestyle changes, 10% concerned intervention with enhanced physical activity and 30% concerned pharmacological or surgical intervention of some form (329) (1a), weight loss was greatest after surgery (−26 kg), followed by dietary intervention (−9.1 kg) and lifestyle changes + diet (−8 kg). The high weight loss achieved in the dietary intervention studies was primarily attributable to VLCD studies.

Subconclusion
- Dietary change is an important component as regards weight loss (1a).

4.1.25 Overall subconclusions on the significance of weight loss in the treatment of Type 2 diabetes
- Dietary change plays an important role in weight loss (1a).
- The effect of weight loss on glycaemic regulation is directly proportional to the magnitude of the weight loss, and the patients responding best to a weight loss are those patients with the highest initial blood glucose levels (1b).
- If normalisation of glucose is the therapeutic goal, the weight loss required is often so great that it is unrealistic for most patients. For the majority of patients a realistic weight loss is 5-10% of the starting weight (1a).
- There are strong indications that both weight loss and calorie restriction contribute to improvement in glycaemic regulation, and that calorie restriction results in rapid improvement in glycaemic regulation before weight loss has been achieved (3b).
- In extremely overweight persons, large weight losses can be achieved through surgery and result in improved glycaemic regulation lasting for several years in Type 2 diabetes (3b). The patients will often experience remission of their diabetes after surgery (4).
- VLCD is effective in inducing weight loss but after 1-2 years, maintenance of weight loss is no better than with a hypocaloric diet (1b).
- The effect of various lifestyle changes involving diet, exercise and behavioural changes differ markedly in relation to weight loss and glycaemic regulation (1a).
- A weight loss of 5-10% has a significant effect on glycaemic regulation. The best predictors of the effect of weight loss on glycaemic regulation are the glycaemic response to a weight loss of only 2.5 to 4 kg after 1-2 months (2b).
- Further research is necessary in order to elucidate why it is more difficult for Type 2 diabetes patients to lose weight than for persons without Type 2 diabetes (5).
- The effect of lifestyle changes on glycaemic regulation is transient and has often disappeared after 6-12 months if it is not followed up by frequent regular controls (1b).
- One to two outpatient check-ups by a clinical dietician probably have no long-term effect on attainment and maintenance of the therapeutic goals (1a).

4.1.26 General dietary advice for the treatment and prevention of Type 2 diabetes
- The dietary recommendations pertaining to the population in general also pertain to persons with Type 2 diabetes.
- Dietary guidance and other lifestyle changes should be life-long.
- Meal frequency – three main meals or minor meals and inter-meal snacks – has no effect on the glucose, lipid and insulin responses.

Carbohydrates
- Carbohydrates from cereals, fruit, vegetables and milk (low fat content) are important components of a healthy diet.
The total content of carbohydrates in a meal is more important for the glycaemic response than the type of carbohydrate.

Sucrose does not increase the glycaemic response more than an isocaloric amount of starch and can be used as a substitute for other carbohydrates.

Artificial sweeteners are safe when consumed in amounts within the recommended limits.

There is no indication for recommending a diet with a low glycaemic index as the primary strategy in a dietary change as diets with a low glycaemic index have little or no beneficial effect on glycaemic regulation.

As with the population in general, consumption of a diet with a high fibre content is recommended, but there is no indication that Type 2 diabetes patients should consume a larger amount of fibre than persons without Type 2 diabetes.

Patients on insulin treatment should try to consume the same amount of carbohydrates from day to day.

Carbohydrates and monounsaturated fat should comprise approx. 60-70% of the daily caloric intake.

Sucrose and food containing sucrose should be consumed in the context of an otherwise healthy diet.

**Protein**

- Consumption of protein does not increase the blood glucose level.
- Type 2 diabetes patients have the same protein requirement as persons without diabetes. Patients with Type 2 diabetes can consume normal amounts of protein unless renal function is impaired.
- The long-term effect of diets with a high protein content is unknown.

**Fat**

- No more than 10% of energy intake should derive from saturated fat, and patients with high LDL cholesterol can benefit from further reducing their intake of saturated fat.
- Recommended cholesterol consumption is <300 mg per day.
- Consumption of trans fatty acids should be limited.
- Diets with a low fat content contribute to a moderate weight loss and a reduction in LDL cholesterol.
- Polyunsaturated fatty acids can comprise approx. 10% of the energy intake.

**Vitamins and minerals**

- There is no indication for vitamin supplement in patients with Type 2 diabetes. As with the remainder of the population, specific amounts of calcium are recommended to reduce the occurrence of osteoporosis.
- It is not recommendable to supplement the diet with additional antioxidants.

**Alcohol**

- It is recommended that Type 2 diabetes patients follow the general guidelines from the National Board of Health concerning the consumption of alcohol (women <14 drinks per week, men <21 drinks per week).
- Patients with neuropathy and pancreatitis should restrict their alcohol consumption.

**Hypertension**

- Weight loss entails a fall in blood pressure.
- Diets with a low fat content that include fruit and vegetables reduce blood pressure.
- In hypertensive Type 2 diabetes patients, reducing salt intake leads to a fall in blood pressure.
- An intake of less than 6 g sodium chloride per day is recommended.

**Dyslipidaemia**

- Saturated fat and trans fatty acids should be reduced to less than 10% of the energy intake.
- In Type 2 diabetes patients with diabetic dyslipidaemia (high triglycerides, low HDL cholesterol and increased occurrence of “small, dense” LDL particles), improvement in glycaemic regulation, weight loss, restriction of saturated fat and increased physical activity have a favourable impact on the lipid profile.

**Nephropathy**

- Protein restriction to 0.8-1.0 g per kg body weight per day in patients with microalbuminuria and to 0.8 g per kg body weight per day in patients with nephropathy reduces the progression of nephropathy.

**Overweight**

- Reduced energy intake with weight loss improves insulin sensitivity and glycaemic regulation.
- Structured programmes, that in addition to dietary change with reduced energy and fat intake also
encompass increased exercise and frequent patient contact can result in a weight loss of up to 5-10\% of the starting weight.

- Exercise is of significance for maintaining a weight loss.
- Dietary change without lifestyle changes do not result in a long-term weight loss.

### 4.1.27 Current dietary recommendations

There is thus no indication for changing the current dietary recommendations. The treatment guidelines used in the dietary treatment of Type 2 diabetes were revised in 2001, but are still based on the recommendations from 1992 (published and revised by the Danish Diabetes Association). The guidelines apply to adults and to children over three years.

### 4.2 Self-monitoring of blood glucose

Even though self-monitoring of blood glucose to facilitate glycaemic regulation is regarded as an important part of diabetes treatment, including in Type 2 diabetes, only a few randomised, controlled trials (RCTs) have addressed this issue exist. Semi-quantitative visually read urine glucose measurements were formerly used for self-monitoring, but in recent decades these have been replaced by blood glucose measurements made on blood glucose meters, firstly in Type 1 diabetes, and later in Type 2 diabetes.

#### 4.2.1 RCTs and meta-analysis

Three independent reviews of the effect of self-monitoring in Type 2 diabetes (371-374) (1a), including one meta-analysis (373, 374) (1a), each conclude that there is no measurable effect of self-monitoring of glycaemic regulation.

For the meta-analysis, Coster and co-workers identified 8 RCTs and 10 non-RCTs on the value of self-monitoring in Type 2 diabetes. Only 6 RCTs (375-380) (1b) were found to be suitable for inclusion in the meta-analysis (373, 374) (1a). In one of the studies, 50\% of the patients were insulin-treated (375) (1b), while the remainder were diet- and/or tablet-treated patients. Age and diabetes duration and severity varied (if stated). The studies are described in more detail in Annex 5.

None of the 6 RCTs revealed any significant effect of self-monitoring (375-380) (1b).

The meta-analysis of the 4 RCTs that investigated the effect of self-monitoring of blood or urine glucose versus no monitoring (375-377, 380) (1b) in a total of 285 patients followed for 3-12 months revealed a statistically insignificant, \(-0.25\%\) estimated reduction in glycosylated haemoglobin (95\% confidence interval \(-0.61\) to \(+0.10\%\)) in the monitoring group (373, 374) (1a) (Annex 5, Figure 1).

The meta-analysis of the 3 RCTs that investigated the effect of self-monitoring of blood glucose versus urine glucose (377-379) (1b) in a total of 278 patients followed for 3-6 months revealed a statistically insignificant, \(-0.03\%\) estimated reduction in glycosylated haemoglobin (95\% confidence interval \(-0.52\) to \(+0.47\%\)) in the blood glucose self-monitoring group (373, 374) (1a) (Annex 5, Figure 1).

It has been suggested that self-monitoring of blood glucose (instead of urine glucose or no monitoring) can help patients to avoid hypoglycaemia (381) (4), but none of the RCTs mentioned address this aspect. In a study in which the patients had to indicate which monitoring method they preferred, 70\% chose monitoring of urine glucose (379) (4). Quality of life does not change with self-monitoring (375, 379, 380) (1b). Self-monitoring of blood glucose is more expensive than self-monitoring of urine glucose (378, 379) (1b), and the relation between the possible medical and economic advantages of self-monitoring of blood glucose are unclear (382).

The negative conclusions of the meta-analysis with respect to the value of self-monitoring in Type 2 diabetes per se and to the value of self-monitoring of blood glucose rather than urine glucose should be evaluated with caution (374) (1a):

1) The statistically strength of the studies is low. In the meta-analysis it is thus estimated that self-monitoring of blood or urine glucose (relative to no measurement) can be associated with a 0.6\% reduction in glycosylated haemoglobin (373, 374) (1a), which should be compared with the UKPDS in which a
difference in glycosylated haemoglobin of 0.9% maintained for 10 years was associated with a 21% reduction in “any diabetes-related endpoint” (383) (1b).

2) The quality of the studies is modest. All the RCTs are characterized by short duration and poor description of the intervention, which varies and is often complex.

3) The patients were only instructed to change the treatment as a result of the monitoring results in a few of the RCTs.

4) The RCTs only include few endpoints. Quality of life and patient satisfaction have not been fully evaluated, and the possible benefit of self-monitoring, e.g. psychologically or as a motivating factor, has not been investigated.

The meta-analysis therefore must be interpreted such that self-monitoring as an isolated treatment modality is not suited to reducing glycosylated haemoglobin. Moreover, it has to be stressed that all the RCTs were carried out before the results of the UKPDS became available in 1998 (383) (1b), and it is therefore uncertain whether self-monitoring of blood glucose can support the treatment of Type 2 diabetes with the current more strict requirement as to glycaemic regulation.

No solid data from RCTs are available to support the assumption that self-monitoring has a greater effect if the health personnel follow up on the method through advice on self care, in which self-monitoring of blood glucose is usually a part12. A sufficiently large and long RCT of the effect of self-monitoring of blood or urine glucose in Type 2 diabetes is therefore desirable, but hardly possible at present.

4.2.2 Other investigations with a large number of patients

Three studies – a cross-section study (384) (4), a registry study (385) (2b) and a questionnaire survey (386) (4) – all of which appeared after publication of the UKPDS (383) (1b) – have assessed the effect of self-monitoring of blood glucose in large, (according to author assumption) relatively unselected patient populations. These studies are characterized by a weaker design than the above-mentioned RCTs (which are of poor quality themselves), but this is to some degree counteracted by the large number of patients.

The German cross-section study encompassed 842 insulin-treated Type 2 diabetes patients and assessed the relationship between self-monitoring of blood glucose and HbA1c (384) (4). The frequency of self-monitoring and HbA1c were found to be negatively correlated, while the frequency of self-monitoring and the frequency of self-adjustment of the insulin dose were positively correlated. These correlations were only occurred in the subpopulation that had undergone a structured treatment and education programme, however.

In the American registry study encompassed 23,153 Type 2 diabetes patients (insulin and tablets: 24%; tablets alone: 55%; diet alone: 21%) and the patients were subdivided according to consumption of test strips for self-monitoring of blood glucose and HbA1c (385) (2b). The study was based on the 1997 American Diabetes Association (ADA) recommendation that pharmacologically treated (insulin and/or tablets) Type 2 diabetes patients should measure blood glucose once daily: The ADA does not make any recommendations regarding self-monitoring in non-pharmacologically treated Type 2 diabetes patients. In the study, pharmacologically treated Type 2 diabetes patients using ≥0.75 strips per day are designated as complying with the recommendation.

The mean value for HbA1c was 0.6 percentage points lower in the 3,011 (54%) insulin-treated patients who complied with the ADA recommendation on self-monitoring than in the patients who did no do so. Correspondingly, HbA1c was 0.6 percentage points lower in the 2,543 (20%) tablet-treated Type 2 diabetes patients who complied with the recommendation. In the 1,967 (41%) diet-regulated patients who carried out “occasional” self-monitoring, HbA1c was 0.4 percentage points lower than in the patients who did not perform self-monitoring. In the patients who monitored, other forms of self care were more frequent and their lifestyle was healthier.

The authors therefore conclude that frequent self-monitoring (as an integral part of the diabetes treatment) is accompanied by better glycaemic regulation, irrespective of treatment form (and of type of diabetes, in that similar results were seen in Type 1 diabetes) (385) (2b).

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12 A common definition of self care is that the patient has to be able to make rational clinical decisions on a rational foundation based on motivation, adequate information, self-monitoring of blood glucose and professional support.
An Italian questionnaire survey on self-monitoring of blood glucose and quality of life was answered by 2,855 (80%) of the 3,567 (80%) Type 2 diabetes patients contacted (20% in insulin treatment alone or combined with tablets) from 101 outpatient clinics and 103 general practitioners (386) (4). The patient population was subdivided according to frequency of self-monitoring: ≥ once per day (17%), ≥ once per week (31%), < once per week (14%) and never (38%). Self-monitoring was more frequent in women (odds ratio (OR) 1.35), in insulin-treated patients (OR 2.86 for insulin alone and OR 2.27 for insulin in combination with tablets), in patients who had had symptoms of hypoglycaemia (OR 2.86), and in patients who adjusted the insulin dose themselves (OR 2.31).

Among the insulin-treated patients, no relationship was found between HbA1c and the frequency of self-monitoring. However, HbA1c was lower in patients who both monitored and adjusted the insulin dose themselves (≥ once per day: 7.5%; ≥ once per week: 7.8%; < once per week: 7.9%) than in patients who did not adjust the insulin dose themselves, irrespective of whether the latter patients monitored or not (8.3%). Among non-insulin-treated patients, HbA1c was higher in the patient groups that monitored the most frequently (both ≥ once per day and ≥ once per week). The quality of life diminished (increased occurrence of frustration, worry and depressive symptoms) with increasing frequency of monitoring in the non-insulin-treated patients, while the quality of life did not change in insulin-treated patients.

The authors therefore concluded that self-monitoring is only effective in insulin-treated Type 2 diabetes patients able to adjust insulin the dose themselves (13% of the population and 66% of the insulin-treated patients). Self-monitoring has no effect in insulin-treated patients who do not adjust insulin dose themselves. Self-monitoring is accompanied by poorer glycaemic regulation and quality of life than in non-insulin-treated Type 2 diabetes patients undergoing dietary treatment alone or in combination with tablets.

The limitations of the study are the design (questionnaire instead of RCT), the lack of objective documentation for the self-reported frequency of self-monitoring and the lack of information on whether the non-insulin-treated patients were instructed in how to adjust diet, exercise and the medical antidiabetic treatment on the basis of the self-monitoring.

4.2.3 Subconclusion

- The value of self-monitoring of blood glucose or urine glucose in the treatment of Type 2 diabetes is poorly documented.
- There is no evidence that self-monitoring of blood glucose as an isolated treatment form has any general effect (1a).
- Provided the patients adjust the insulin dose themselves, self-monitoring of blood glucose does have an effect (4).
- Better documentation for an independent effect of self-monitoring of blood glucose in Type 2 diabetes is unlikely to be forthcoming, however, as large-scale studies of the value of self-monitoring are unlikely to be initiated, among other reasons in view of the results of the UKPDS (5).
- If self-monitoring of blood glucose is to have an optimal effect, a minimum requirement is for this treatment modality to be integrated with the other non-pharmacological self care behaviour in Type 2 diabetes (5).
- Even though self-monitoring of blood glucose per se does not have any effect on HbA1c, it is still a useful tool in relation to self care. For example, it shows the patient how the diabetes reacts to changes in diet and exercise. The measurements can be a help to identify lifestyle changes that optimise metabolic regulation, and the detection of increasing values can help motivate lifestyle changes (5).
- The measurements are often of great value in patients with intercurrent disease, where they can be decisive determinants of whether the patient can remain at home or has to be admitted to hospital (5).

4.3 Exercise and Type 2 diabetes

Type 2 diabetes is closely associated with the occurrence of the metabolic syndrome which, in addition to diabetes, includes obesity, hypertension and dyslipidaemia. As components of the metabolic syndrome all comprise risk factors for cardiovascular disease, the present section examines the effects of physical exercise on all components of the metabolic syndrome.

In Denmark and Europe, the metabolic syndrome is defined by the presence of a number of components (2) (1a) that will also be used in the following with the addition of measured insulin resistance.
The effect of physical exercise has been investigated in a number of original studies (Annex 6), all of which include patients with Type 2 diabetes mellitus. The studies employed aerobic, dynamic training (endurance training). The duration and intensity of the training is shown in Annex 6.

4.3.1 Effects of physical training

The effect of physical training on HbA1c or fasting blood glucose

The effect on glycaemic regulation has been examined in a meta-analysis of 14 trials (11 randomised and 3 non-randomised) (387) (1a) that encompassed a total of 504 patients. It was found that physical training led to a 0.66 percentage point decrease in HbA1c. No difference in fall in HbA1c was detected between fitness training and aerobic training.

The effect of physical activity on fasting insulin

There is no evidence for any effect of physical activity on fasting insulin.

The effect of physical training on insulin resistance/insulin sensitivity

Three intervention studies have demonstrated unchanged insulin resistance after physical training (388-390) (1b), while one study has demonstrated a fall on insulin resistance (391) (1b). The latter is supported by the findings of a case control study (392) (3b), which also demonstrated decreased insulin resistance in connection with physical training.

The effect of physical training on the lipid metabolism

In 5 out of 6 controlled studies, physical training reduced the triglyceride concentration in the blood (389, 393-396) (1b), but had no effect in one study (359) (1b).

In 5 studies, total cholesterol was unchanged with physical training (359, 389, 394, 396, 397) (1b) while HDL cholesterol was unchanged in 4 (359, 389, 396, 397) (1b) and increased in one (394) (1b).

The effect of physical training on the blood pressure

There are no randomised, controlled studies demonstrating any effect of physical training on blood pressure (359) (1b). A few studies of lower evidence grading show both unchanged (398) (3b) and lower blood pressure (392, 399, 400) (4).

The effect of physical training on weight change

No studies exist that unambiguously show the effect of physical training on body weight under constant energy intake as this has rarely been recorded in the studies. Of the studies with the highest evidence grading, approximately half conclude that energy intake increases corresponding to the increased energy consumption necessitated by the physical training, with weight consequently remaining unchanged (387) (1a) (359, 389, 393, 395) (1b). In the other half a weight loss is seen, thus indicating that the increased energy consumption is not fully compensated for by an increased energy intake (280, 388, 394, 396, 397) (1b). Accordingly, waist measurement was unchanged in two studies (389) (1b) (391) (2b), while one cohort study (391) (2b) and two cross-section studies report a decrease in waist measurement (398, 401) (3b), which indicates a favourable change in body composition.

The effect of physical training on the maintenance of weight loss

In has been demonstrated that exercise alone only leads to a minor weight loss (402) (1a). Two of the studies in this meta-analysis found a greater effect of dietary change in combination with exercise relative to dietary change alone (402) (1a). Similarly, exercise seems to be of great importance for the maintenance of a weight loss over a longer period (403) (1a).

4.3.2 Subconclusion

- Physical activity improves the regulation of blood glucose (1a).
- There is evidence for both unchanged (1b) and reduced (1b) insulin resistance after physical activity.
- Physical activity reduces the blood level of triglycerides (1b), while the total cholesterol remains unchanged (1b).
- There is no evidence that physical activity per se changes the blood pressure (1b).
- Physical activity results in either unchanged (1b) or lower weight (1b).
- Physical activity is of importance for maintenance of weight loss (1a).
4.4 Smoking and diabetes

The number of studies focusing on smoking and diabetes is small and they often do not differentiate between Type 1 and Type 2 diabetes. Intervention studies are particularly lacking (404) (1b). Effects of nicotine in the form of raised mood level, exaltation, sedative or anxiolytic effects and habitual smoking in relation to every-day social situations explain part of the addiction and the unwillingness to cease smoking.

Smoking can be associated with diabetes. The relative risk of Type 2 diabetes among women (405) (2b) and men (406) (2b) who smoked more than 25 cigarettes per day was 1.42 and 1.94, respectively, compared with non-smokers. Young onset of smoking and the number of cigarettes are risk factors for development of diabetes (407) (2b).

Insulin resistance in Type 2 diabetes has been found to be raised in smokers (408) (3b), just as smoking has been found to be a marker for insulin resistance associated with abdominal obesity (409) (2b). The effect of smoking on metabolic regulation has mainly been investigated in Type 1 diabetes, and has not yet been clarified, although smoking was found to be one of the strongest predictors for poor metabolic regulation in Type 1 diabetes (410) (2b).

Type 2 diabetes is associated with increased morbidity and mortality due to cardiovascular disease. In several studies, cigarette smoking has been shown to comprise a significant risk factor for death from ischaemic heart disease in Type 2 diabetes (411-413) (2b). Smoking increases the frequency of macrovascular complications (414, 415) (1b) (416) (2b) (417) (2c). Ischaemic heart disease was 1.54 times more likely among former smokers than among non-smokers (418) (2c). Cigarette smoking comprised an independent risk factor for stroke (419) (2b). Mortality among Type 2 diabetes patients who had ceased smoking more than 10 years earlier was 25% greater than among non-smokers, but significantly lower than among diabetes patients who had stopped within the past 9 years (420) (2b).

Smoking increases the risk of microalbuminuria in Type 2 diabetes (421) (4). The incidence of micro- and macroalbuminuria was significantly higher in smokers (53%) than in former smokers (33%) and in non-smokers (20%) (422) (2c). The findings have been confirmed by others (423) (2b) (424, 425) (2c). Smoking is described as a risk factor for neuropathy in both Type 1 and Type 2 diabetes (426, 427) (2c). Current or former smokers had neuropathy significantly more frequently than diabetes patients who had never smoked (428) (3b). Patients who smoked 30 packets or more per year had a relatively risk of 3.32 for neuropathy compared to patients who smoked less (428) (3b). A prospective study showed a 2.2-fold higher incidence of distal neuropathy in smokers than in non-smokers (429) (2b). Patients in whom neuropathy was present at the onset of Type 2 diabetes were 12 times more likely to be smokers than non smokers (429) (2b). The relation between smoking and retinopathy has not yet been clarified (423) (2b).

It is well known that cessation of smoking reduces the risk of cardiovascular disease, cancer, stroke and pulmonary diseases. In contrast, there is very limited evidence about smoking cessation in diabetes patients (404) (1b). Earlier results have been disappointing (430) (1b) (431) (2b), even though positive results are seen (432) (1b). Clinical practice guidelines on smoking cessation in persons without diabetes based on a meta-analysis of randomised, controlled studies of at least 5 months duration published in peer-reviewed journals between 1974 and 1995 were published in 1996 (433) (1a). Every healthcare worker can contribute to smoking cessation, and the more people who encourage a smoker to stop smoking, the better the result. The encouragement has to be given directly, either individually or in groups, and there is a strong dose-response relation between intensity of personal contact (433) (1a) (434) (2c) and between duration of treatment with many personal contacts (433) (1a) (404) (1b) and smoking cessation. Nicotine chewing gum improves smoking cessation by 40-60% after 1 year and is more effective than other control interventions, irrespective of the intensity (433, 435-438) (1a). Transdermal nicotine doubles the likelihood of abstinence after 6 months (437) (1a). The effect of antidepressants is inconclusive (433), but a double-blind study of bupropion revealed significantly greater smoking cessation after 1 year (19-23%) than with placebo (12%) despite a lower weight increase (439) (1b). Questionnaire surveys showed that 41% of diabetes patients are not recommended to cease smoking by their general practitioner (440) (2c), among other reasons due to lack of time or payment and low expectations as to the result of the advice (441, 442) (4). In concert with this the results of two prospective, randomised studies of smoking cessation among diabetes patients were disappointing (430) (1b) (431) (2b).

In a Danish general practice study in which the patients were followed for 6 years, the prevalence of smokers was reduced from approx. 35% to 30% after 6 years (331) (1b). In the Steno 2 study the prevalence of
smokers fell from approx. 27% to 21% after 4 years. The reduction in the number of smokers was the same in the group that was followed in general practice and at the Steno Diabetes Centre (334) (1b). For many years, analyses have confirmed that advice on smoking cessation is one of the most cost-effective interventions (443-445) (1b). Even though no cost-benefit analyses exist for diabetes patients, it can be assumed from the above that cessation of smoking will be extremely cost-effective among this high-risk group. Paradoxically, cessation of smoking is accorded low priority among diabetes patients when different aspects of diabetes treatment are assessed (446) (2c). One of the reasons is the risk of an estimated 2.5-4.5 kg weight gain upon cessation of smoking, and in 10% of men and 13% of women as much as 11 kg (447) (2b). Depression and dysphoria are more frequent among smokers than among non-smokers, and smokers with depression have more difficulty in stopping smoking (448) (5). Diabetes patients have a greater risk of depression than a comparable population group (449) (3a) (450) (4). Only few data are available on this matter among diabetes patients. A single study found that the number of cigarettes and level of depression were correlated (451) (2c). Finally, hospitalisation for complicating disease does not seem to enhance the motivation to cease smoking among diabetes patients (452) (2c).

**Subconclusion**

- Smoking increases the risk of developing diabetes (2b).
- Smoking exacerbates both the macroangiopathy (1b) and the microangiopathy (2b).
- Efforts to achieve smoking cessation in patients with diabetes seem to be very modest (2c).
- Smoking cessation counselling must be expected to be cost-effective (1b).
- Diabetes patients accord low priority to smoking cessation, partly because of the risk of weight gain (2b) and the development of depression (3a).

### 4.5 Education

Education of the Type 2 diabetes patient is regarded as one of the cornerstones of diabetes treatment. The aim is to strengthen the patient's knowledge of diabetes and practical skills such as blood glucose monitoring, foot care, shopping and food preparation in order to achieve permanent lifestyle changes and to improve the patient's quality of life. This information-based partnership between the patient and the diabetes team can thus help the patient to understand his disease, to take responsibility for it and to participate more in its treatment (self care).

No Danish data are available concerning assessment of the value of education. It has therefore been necessary to look abroad for literature on the topic. The present chapter particularly focuses on the effect of education on HbA1c, blood pressure, weight, blood lipids, late diabetic complications and quality of life. In contrast to the education offered to Type 1 diabetes patients, education of Type 2 diabetes focuses to a far greater degree on lifestyle changes in relation to diet, exercise and weight loss. In the present review of education of Type 2 diabetes patients only examines clinical controlled trials, of which not all are randomised, and meta-analyses.

Sixteen studies that include Type 2 diabetes patients have been identified. They fall into two types of study. In one type, broadly orientated education on Type 2 diabetes is given. In the other, the focus is on lifestyle changes via changes in diet and exercise habits.

The first group encompasses 8 studies (453-458) (1b) (459) (3b) (460), of which 6 are randomised clinical trials (RCTs) (453-458) (1b). In the 6 RCTs the number of patients varied from 51 to 256. Three of the studies were carried out in the primary sector, two in the secondary sector, and one at a university hospital. The age group was primarily the 55-65-year-olds with diabetes of 5-10 years duration except for 2 studies that focused on patients with shorter disease duration (454, 456) (1b). The quality of the studies is generally poor with methodological and conceptual weaknesses. Thus the method used to randomise the patients is not described, and correct “intention to treat” analysis was only employed in one study (453) (1b). Likewise, the description of the patients and the education is extremely inadequate (453-457) (1b) (459, 460) (1b). The education was generally provided by a doctor, nurse or clinical dietician. The number of hours of education varied from 4 to 52, and the duration of the educational programmes ranged from 3 weeks to 2 years. None of the studies aimed to teach the patients to regulate pharmacological treatment themselves.

Three studies found a significant difference between the intervention and the control group as to glycaemic regulation assessed from HbA1c (453, 455, 457) (1b). The difference varied from 0.75 to 1.35 percentage
points. These 3 studies are characterised by the fact that the education stretched over a longer period and had the shortest time intervals between cessation of education and evaluation of the effect. Fewer patients in the intervention groups were treated with peroral antidiabetics. In the other studies there was no difference in HbA1c between the intervention and the control group. Moreover, the effect of education characteristically decreased with time from cessation of the education, and had disappeared after 6 to 48 months, except in one study (454) (1b). The studies that detected a difference were based on frequent contacts at intervals ranging from one (453) (1b) to four months (455, 457) (1b). Two studies evaluated the effect of education on blood pressure (454, 455) (1b), one of which reported a positive effect (5-7 mmHg). In four of the eight studies the weight loss was significantly greater in the intervention group than in the control group, albeit that the difference was small (456, 457, 459) (1b) (460) (3b). The studies (453-455, 457) (1b) focused on lipid status; in one study, serum cholesterol and triglycerides were found to have decreased following education. There was no evidence of any effect on the occurrence of late diabetic complications. Three studies investigated quality of life (454, 455, 459) (1b). Only one of these used a validated method to evaluate the quality of life. In that study, no improvement was found in the quality of life of the intervention group, whereas deterioration was recorded in the control group. Education led to greater knowledge of diabetes (455, 459) (1b). One study suggested that education can lead patients to better accept their diabetes (458) (1b).

The studies thus show a limited effect on HbA1c and virtually no effect on weight. Education enhanced knowledge of diabetes. In order for an educational programme to have any effect over a longer period, contact with the diabetes team seems to be necessary at intervals of no more than 3-4 months.

Eight studies, of which seven were RCTs, focused on dietary change, exercise and self-monitoring of blood glucose (360, 375, 461-465) (1b). The studies are all of poor quality, with the form and content of the education being particularly inadequately described. The education lasted from 9 to 20 hours and stretched over a period of up to 20 months. Approximately half of the studies detected an improvement in HbA1c, but no effect on blood pressure. Five studies reported BMI and did not find any difference between the control and intervention groups. No difference was found in the lipid profile, either.

Three randomised controlled studies (466-468 (1b)) included both Type 1 and Type 2 diabetes patients. In this case too, the studies are of poor quality, the intervention is poorly described, and data are not presented separately for Type 1 and Type 2 diabetes. As above, the conclusion reached is that it is difficult to determine which form of education has the greatest effect on the treatment of Type 2 diabetes patients.

Meta-analyses and reviews of the effect of education in Type 2 diabetes

Five large meta-analyses and reviews have examined the value of education in Type 2 diabetes. In the review by Norris and co-workers (330) (1a), 72 studies were analysed. Education was found to have short-term effects (less than 6 months) on knowledge about diabetes, self-monitoring of blood glucose, self-reported dietary habits and glycaemic regulation. The analysis also showed that enhanced knowledge of diabetes or the use of computers in the educational programmes did not lead to improved glycaemic regulation. Several studies illustrated that follow-up of education at intervals of weeks to months improved knowledge about diabetes and diet. Frequency of contact and especially the overall duration of the education were important determinants of the effect of the education. When the follow-up interval was long the effect of the education decreased or it had no effect. The effect on lipids, exercise, weight, blood pressure and quality of life varied, and there was no effect on cardiovascular complications or mortality. The studies that primarily focused on lifestyle changes did not reveal any certain effect on glycaemic regulation. None of the studies included any form of health economic analysis.

A later meta-analysis by Norris and co-workers (469) (1a) encompassing 31 RCTs assessed the effect of education on glycaemic regulation. The improvement in HbA1c immediately after cessation of education, which consisted of an average of 6 contacts over a period of 6 months, was 0.76 percentage points. Four months later the fall in HbA1c had decreased to 0.26 percentage points. The effect on HbA1c correlated to the number of contacts and the total contact time between the diabetes team and the patient. On average, a patient had to be seen for 24 hours to achieve a 1 percentage point improvement in HbA1c. The effect on HbA1c could not be related to education method, the focus of the education (knowledge versus lifestyle), group versus individual education, or to which person in the diabetes team provided the education. In most of the studies the intervention groups had longer contact time with the diabetes team than the control groups. In the meta-analysis it was not possible to differentiate between the effect of education per se and the contact time. A newly published review by the Alberta Heritage Foundation for Medical Research (470) concluded
that no conclusion can be drawn as to “which types of programs or what components are most effective in improving the ability of adults with type 2 diabetes to self-manage their disease in the long-term”.

Brown (471-473) (3b) and Padgett and co-workers. (474) (1a) found that education was positive in relation to knowledge about diabetes, self-care, insulin injections, weight loss, glycaemic regulation and quality of life. These reviews did not differentiate between Type 1 and Type 2 diabetes patients, however. Padgett concluded on the basis of 93 studies that education had a positive effect on knowledge about diabetes and diet. The effect on weight and glycaemic regulation was less pronounced and disappeared with time after cessation of the education (474) (1a). The effect on HbA1c was maximal after 6 months and had disappeared after 12 months (474) (1a). In Padgett’s meta-analysis of 94 studies the effect of education was found to be independent of the form of education. Knowledge about diabetes and practical skills increased with the duration of the education, and this effect was significantly greater than the effect on weight, blood pressure and lipids. Self-reported effects on diet etc. were also greater than objective, measured effects such as weight (473) (3a). Side effects of the education have not been addressed in the above-mentioned literature.

Comments
It is difficult to draw any general conclusions from these meta-analyses due to the inadequate design of the individual studies and to the fact that the studies included in the analyses are very heterogeneous and the results poorly presented. Moreover, many of the studies have not been published. The unpublished studies and studies of poor quality generally show the greatest benefits of education, especially studies without control groups. In the 1990 analysis by Brown comprising 82 studies (32% unpublished), 56% thus lacked a control group and only 29% were RCTs. A further difficulty in drawing conclusions is publication bias, positive studies being more likely to be published than studies that have not revealed any effect of education. Moreover, the studies are characterized by a high dropout rate among the patients. It should be noted that one of the reasons for the vague conclusions is the poor description of the form and content of the education in the studies. Moreover it will often be difficult to demonstrate an effect of education in patients undergoing pharmacological treatment as it is traditionally the physician who changes the medication and not the patient. This is probably also the reason why education has been found to have a greater effect on glycaemic regulation in Type 1 diabetes, where the patient actively participates in the treatment and is able to improve glucose control by changing the insulin dose. It is characteristic that in the studies where education has an effect, this is found immediately following cessation of the intervention and decreases with time. The meta-analyses primarily derive from the USA, where the health system is differently organised. Together with cultural and socio-economic differences, this makes it difficult to extrapolate the conclusions to Danish conditions. There is therefore a need for Danish (European) long-term RCTs that follow guidelines such as described by Moher and co-workers. (475). No evidence is presently available that diabetes schools have any effect.

Subconclusion
- The effect of education on diabetic regulation expressed as HbA1c, lipid status and weight is limited (1b).
- Education has effects on knowledge about diabetes and practical skills (1b).
- Education is better than no education (1b).
- The effect diminishes with time following cessation of education (1b).
- Education does not have any demonstrable effect on the late complications of diabetes (1a).
- It is not possible to identify which forms and methods of education yield the best results, although the number of contacts and the contact time with the diabetes team seem to be of significance for the effect (1a).
- No standards exist for the content of educational programmes.
- There is a need for more research and research of high quality into the effect of education in Type 2 diabetes (5).
- No documentation is available indicating any effect of diabetes schools.

4.6 Shared care

The term “shared care” within diabetes treatment was suggested in 1971 (476) (4). However, it is within the last ten years that the term has been used regularly in connection with treatment of chronic diseases such as asthma, hypertension, rheumatoid arthritis and diabetes mellitus.

No clear definition of the term exists. According to the most used definition: “Shared care is the joint participation of hospital consultants and general practitioners in the planned delivery of care for patients with
a chronic condition, informed by enhanced information exchange over and above routine discharge and referral notices” (477) (4).

The definition underlines the planned cooperation and an overall and intensive information exchange between the two sectors.

In Denmark, the treatment of Type 2 diabetes patients has traditionally been the responsibility of general practitioners. It was not until serious complications arose that the patient was transferred to the hospital system. The increasing awareness in recent years that complications can be prevented through intensified treatment has brought the expert knowledge of the secondary sector more into focus among Type 2 diabetes patients.

The motives for shared care differ:

- A desire to optimise utilisation of the economic resources. With the present increasing number of new cases of Type 2 diabetes one must expect increased expenses in the secondary sector for treatment of complications. If shared care can avoid some of these complications and hence avoid hospital admissions, this can be economically attractive.
- Awareness that there is insufficient capacity to treat all Type 2 diabetes patients at specialist level.
- A belief that the general practitioner's training in communicating with diabetes patients and their knowledge of diabetes patients and their conditions of life combined with the expert knowledge of the secondary sector provides the best treatment in that the shared care model is ideal for disseminating new scientific advances via specialists in the secondary sector to general practitioners and to diabetes patients, and vice versa. At the same time, it reduces variation in the level of treatment, and ensures a minimum quality of treatment.

A 1994 review of the literature by Greenhalgh (478) (1a) identified five randomised and controlled studies and several controlled, non-randomised or descriptive studies. None of the randomised, controlled studies found that shared care improved the measured clinical parameters compared with treatment in the hospital sector.

A Scottish prospective, randomised study from 1994 (479) (1b) compared conventional outpatient clinic treatment with shared care. The participating general practitioners had received guidelines, and the content of the check-ups was specified. Following each check up, the information was sent to the outpatient clinic. Computer-generated reminders were included in both groups. 274 diabetes patients (both Type 1 and Type 2) were included. The study ran over 2 years. There was no difference between the groups as regards metabolic regulation, psychosocial status, knowledge about diabetes, opinion about check-ups, satisfaction with treatment, visits outside planned check-ups or morbidity in general. Shared care was equally effective in Type 1 and Type 2 diabetes. Ten percent stayed away from conventional treatment, 3% from shared care. For the diabetes patient shared care was slightly cheaper. The total cost was the same in the two groups. In the shared care group, operation of the clinical database accounted for 30% of the expenses.

The conclusion of the study was that this model for shared care was just as effective as conventional outpatient treatment.

In a 1998 meta-analysis of diabetes treatment in general practice Griffin, (480) (1a) concluded that unstructured treatment yields poorer follow-up and poorer glycaemic regulation.

Shared care can reach a standard that is just as good or better than that of the hospital outpatient clinics, at least in the short term. The meta-analysis can be criticized for only encompassed 5 RCTs of different types – two older British RCTs, two more recent British RCTs and one Australian RCT (479, 481-484) (1b).

In England, from where most of the literature stems, check-ups of diabetes patients have traditionally been performed in hospital outpatient clinics, later on in diabetes clinics. Capacity problems have been the driving force behind the transfer of patients to general practice – in many cases in a form of shared care.

From his literature review Greenhalgh (478) (1a) concluded that provided the care is structured care and help can be obtained from hospital specialists, general practices with a strong interest in diabetes treatment
are probably able to carry out the routine control of selected group of diabetes patients just as effectively as hospital outpatient clinics.

In 1995, Pritchard and Hughes (485) described shared care in general in the health service. Some important elements for successful shared diabetic care seem to be:

- GPs and practice staff who are motivated in improving care for their diabetic patients
- Clear division of responsibility between general practice and hospital teams
- A structured approach to providing general practice-based diabetic care, with clear aims and systematic follow up of patients
- A register of patients with diabetes, preferably computerized, to enable easy recall of patients and facilitate audit
- Patient-held shared care cards or records for good communication
- Access to facilities that are normally unavailable to a practice – dietician, chiropody, laboratory services, specialist nurse advice, retinal screening, education support, etc.
- Support and training for GPs, practice nurses and others to motivate them and keep them in touch with developments in diabetic care
- Ease of communication and close cooperation with hospital clinic or diabetes centre
- Facilitators to help the practice team gain the knowledge, skills and confidence to establish effective diabetic care
- Financial incentives for practices to take on more chronic disease management
- Involvement in audit of diabetic care and encouragement to use findings to continue to improve services.

In a Danish review from 1998 (486) (3b), no Danish publications are referred to. As both the organisation of the health service and the education of general practitioners vary from country to country, the results of foreign programmes cannot be extrapolated to Danish conditions.

A quality evaluation of diabetes care in a major general practice (487) (4) concluded that metabolic regulation and screening for late diabetic complications were not optimal relative to applicable guidelines. It is unlikely that this general practice differs negatively from other general practices in Denmark. Likewise, an analysis of a diabetes clinic (488) (4) found that not all Type 2 diabetes patients were screened for late complications according to the existing framework programme. One method of ensuring improvement could be shared care.

The guidance report to Danish physicians entitled “Type 2 diabetes og det metaboliske syndrom – diagnostik og behandling (Type 2 diabetes and the metabolic syndrome – diagnosis and treatment)” published in the Journal of the Danish Medical Association “Ugeskrift for Læger” (2) did not consider whether the organization of diabetes treatment influences the treatment result.


**Subconclusion**

- Shared care agreements between the primary sector and the diabetes outpatient clinics only exist in a few parts of the country at present (4).
- There is no evidence that shared care is better than treatment solely in the hospital service (1a).
- There is no evidence that shared care is better than treatment solely in the primary sector.

### 4.7 The diabetic foot

This section concerns measures aimed at preventing foot ulcers and amputation, i.e. measures that typically involve patients with Type 2 diabetes. For this reason the “diabetic foot” is described under non-pharmacological treatment. For a discussion of morbidity (when the diabetic foot has become “ill”) the reader is referred to the section on screening for late complications.

Depending on the definition and how it is measured, 20-40% of the Type 2 diabetes patients have peripheral neuropathy (loss of sensation in the feet). A Danish study shows that 83.5% of the Type 2 diabetes patients...
had feet that were at risk of developing foot ulcers, and that 5% had foot ulcers (490). As regards the foot, treatment of Type 2 diabetes entails a strategy for screening for risk factors for foot ulcers and amputation (see Chapter 6) and for preventative measures directed at patients who present with these risk factors.

4.7.1 Package solution: Screening and prevention

There is evidence that a package solution consisting of a simple screening programme combined with necessary measures aimed at at-risk patients reduce the frequency of amputations (491-493) (1b) and skin and nail changes disposing to ulcers (491) (1b). There is also evidence that prophylaxis reduces the number of ulcers in high-risk feet (492, 494, 495) (1b). Finally, a simple programme including screening and prophylaxis is cost saving (493) (1b).

4.7.2 Prevention

The following preventative measures are regarded as necessary:

1) Education
2) Podiatric care (treatment of skin and nails)
3) Therapeutic footwear.

These elements have each been examined in a number of studies, and the evidence for their individual effect is not as strong as for the effect of the full package.

4.7.3 Education

This issue has recently been addressed in a Cochrane review (496) (1a) and in an evidence review in Clinical Guidelines for Type 2 diabetes (497) (1a).

a) Foot ulcers and amputations:
   In at-risk patients the provision of intensive education as compared to the usual information was found to reduce the frequency of ulcers and amputation (492) (1b).
   In not-at-risk patients there was no difference in the frequency of ulcers and amputations (498) (1b).

b) Skin changes (calluses, which predispose to ulcers) under the forefoot reported in two studies were found to be improved after intensive education (499) (1b), but the effect had disappeared after seven years (498).

c) Foot care habits among the patients were found to be improved in three studies (short-term effect investigated) (498-501) (1b).

d) The patients’ knowledge of foot care was found to be enhanced (short-term effect) in three studies (499, 500, 502) (1b). In a single, very small study (501) (1b), no effect was found. After seven years there was no effect (498) (1b).

e) Education in foot care as part of general diabetes education – in contrast to special education – increased the patients’ knowledge, but had no any effect on foot care habits, skin and nail changes or ulcers/amputation (466) (1b). Another study that only registered foot care habits found a short-term improvement (454) (1b).

f) Individual education (1 hour – in contrast to the other studies, which concerned group education in classes) has been examined in two studies (502, 503) (1b). Mazzuca examined the effect of special education undertaken in the primary sector, but did not find any effect. Rettig examined the effect of home education by a nurse and found that this enhanced knowledge (after six months), but had no effect on the way the patients managed foot care and had no effect on the feet.

Subconclusion concerning education

- The Cochrane analysis group expressed the need for better and more uniform studies on larger patient material. The existing studies were unsuitable as the foundation for a meta-analysis.
- Knowledge about foot care and foot care habits seem to be positively affected by education on a short-term basis, though, but they found the documentation for an effect on ulcers and amputations to be too uncertain.

It needs to be stressed that the good results have been obtained through a package solution that includes education. For the time being it seems to be the at-risk patients who benefit from education, while it has been documented that there is no effect in patients who do not (yet) have risk factors for diabetic foot ulcers. Moreover, the effect of individual lessons seems to dissipate in the long term, suggesting that education should be provided continuously (504). There are no studies that can help determine where and by whom the education should be provided.
4.7.4 Podiatric care
Podiatric care comprises treatment of abnormal changes (calluses, corns), fungal infections, foot warts, blisters, nail deformities and general skin care and nail care (cannot be carried out by immobile or weak-sighted persons and not without risk of skin lesions (ulcers) in persons with loss of sensation).

Podiatric care has been examined in several studies of the effect of education as the condition of the feet depends among other things on whether the patient visits a podiatrist (491, 498, 499) (1b). As mentioned earlier, two studies (491, 499) (1b) found a beneficial short-term effect on knowledge, foot care habits and foot condition. Only one study investigated the long-term effect (the patients in Ronnemaas’ study), and here the effect was found to have disappeared after seven years. These patients were not at risk of foot ulcers when they entered the study, however.

The isolated effect of a standardised foot care programme predominantly carried out by podiatrists has been examined in a register study comprising 255,256 patients at risk of amputation due to diabetes, peripheral vascular disease or gangrene (505) (2b). The amputation rate was 4-5-fold higher among the untreated persons, but patients with diabetes was not treated as a separate group.

For ethical reasons, randomised studies comparing diabetes patients with and without podiatric care are unlikely to be carried out as the podiatrist is regarded as a key person in a multidisciplinary foot team (504) (1a) (506) (1a).

4.7.5 Therapeutic footwear
Shoes
Despite the fact that it is basic knowledge and essential that footwear must not be too tight (too short or narrow and/or insufficiently spacious), no studies exist that shed light on how many persons need to substitute their shoes with corrected footwear, special footwear or custom-moulded shoes (orthopaedic footwear). However, one quiet recent Danish study shows that 9% of an at-risk population attending foot clinics in the primary sector use custom-moulded footwear. It is assumed that half of all patients with diabetes are at risk of foot ulcers, and that approx. 5% thus need custom-moulded footwear (507).

Foot deformities, which are frequent among diabetes patients with neuropathy, lead to abnormal pressure on the skin over bony prominences, joint stiffness, joint deformities, calluses, altered skin structure, previous foot surgery and Charcot foot. Incorrect footwear or deficient custom-moulded insoles, foreign bodies in the shoes, injuries and burns, and hyperactivity can give rise to ulcers (504) (1a).

Among at-risk patients it is documented that the frequency of recurrent ulcers (recurrence in the form of new foot ulcers) is markedly reduced with the use of special therapeutic shoes with individual custom-moulded insoles instead of ordinary footwear (495) (1b). In addition, a case control study showed that patients who used special therapeutic footwear had fewer recurrent ulcers than patients who continued with ordinary footwear (495) (3b). Finally, two case control studies in which the use of prescribed therapeutic footwear was quantified showed that there were fewer recurrent ulcers with the appropriate use of the prescribed therapeutic footwear (508, 509) (3b).

Custom-moulded insoles
There are numerous means of making custom-moulded insoles. One study shows that stiff, custom-moulded, insoles are more effective than regular podiatric care (510) (1b), but the study is small, and podiatrists supplement their treatment with custom-moulded insoles. Another study compared two types of insoles (soft insoles versus total-contact insoles) without finding any difference. Thus it is not possible to recommend any one particular type of custom-moulded insole (511) (1a).

Who is going to screen and monitor?
Provided acceptance on the part of the patient and general practitioner and the use of standardized sum-monsing and examination procedures, shared care arrangements between the primary and secondary sectors can be just as effective as regards surveillance of foot problems as secondary sector surveillance alone (512) (1a). It should be noted, though, that early studies included in this review showed a less beneficial effect of the general practitioner. Moreover, multidisciplinary teams were not available at the hospital departments in question. No account was given of results regarding foot disorders, including foot ulcers and amputations.
The cooperation has not been researched in detail, but it is regarded as good clinical practice to focus on communication between the primary and secondary sectors in order to ensure the patients immediate access to necessary treatment. This in turn necessitates unambiguous and “immediate” referral to treatment.

**Multidisciplinary teams**

No scientific studies exist showing that multidisciplinary treatment teams are advantageous relative to other organisation forms, neither in relation to annual screening with preventative intervention nor in relation to treatment of foot complications. However, foot problems are multifactorial and involve podiatrists, nurses, diabetologists, orthopaedic surgeons, vascular surgeons, orthopaedic shoe makers and orthotists, as well as a number of service specialities such as microbiologists, clinical physiologists, nuclear medicine specialists and radiologists, and finally, the primary sector with general practitioners and podiatrists (513). Moreover, the best results expressed in terms of a (very considerable) reduction in leg amputation rate are obtained with multidisciplinary treatment (514, 515) (2b). In recommendations and consensus reports (497, 504) (1a) (513) it is therefore regarded as good clinical practice to arrange multidisciplinary foot teams at different levels. This also facilitates the “immediacy”-principle.

There are no studies showing that centralisation is better than the usual treatment. It must be remembered, however, that organising foot teams in principle implies centralisation and hence an increasing competence among the healthcare professionals. Again, reference is made to the fact that the best results in terms of amputation rate are achieved through multidisciplinary treatment and that from the point of view of continuity and education, it is appropriate to plan multidisciplinary treatment at ulcer centres with clinical expertise in wound healing (516) (4).

### 4.7.6 Subconclusion

- In at-risk patients, education reduces the frequency of ulcers, amputations and the callus formation (1b).
- The patient’s knowledge about foot care is temporarily enhanced by education (1b).
- The amputation rate is 4-5-fold higher in patients that are not regularly examined by a podiatrist (2b).
- Incorrect footwear or the absence of custom-moulded insoles can cause foot ulcers (1a).
- The frequency of recurrent ulcers is reduced considerably through the use of special therapeutic shoes and custom-moulded insoles (1b).
- Shared care and secondary sector surveillance alone are equally effective as regards foot problems (1a).
- Multidisciplinary treatment considerably reduces the frequency of leg amputation (1a).

### 4.8 Organisation

Non-pharmacological treatment is an integral part of the treatment offered to Type 2 diabetes patients in general practice and diabetes clinics. Over the past decades the treatment strategy for the acute treatment of Type 2 diabetes has changed such that the patient is rarely admitted to hospital now. Even with patients who are admitted at the time of diagnosis it is often only a matter of hours to days before they are transferred to outpatient treatment.

As Type 2 diabetes is a lifestyle disease, where overweight is the essential factor, it is decisive that once the patient is diagnosed he/she should immediately be offered a consultation and associated follow-up with a clinical dietician regarding dietary guidance, with a nurse regarding general instruction about the disease, with a podiatrist and with a physician regarding a general health assessment and discussion of possible pharmacological treatment and instruction about the disease. The educational material necessary for instruction and self-study is already available, especially via the Danish Diabetes Association.

The problem is that outpatient clinics are often overcrowded and unable to provide dietary instruction etc., for example due to a shortage of clinical dieticians. A waiting period of several weeks for a consultation with a clinical dietician is unfortunate, especially at the time of diagnosis. The same applies to the inadequate possibilities for general practitioners to refer the patients to a clinical dietician. The shortage of capacity can perhaps be alleviated by establishing diabetes schools where the patients are taught in classes. Irrespective of whether individual or group education is used, it is decisive that an educational programme exists and that a system is employed so that that other members of the diabetes team can see what topics have been taught, and that the patient’s understanding, knowledge and practical skills such as blood glucose self-monitoring are evaluated. Furthermore, it is necessary to continuously monitor patient knowledge and compliance.
General practice has to be able to assume primary responsibility for initial treatment at the time of diagnosis. The treatment presently offered in general practice does not always live up to the standard necessary if lifestyle changes are to be implemented. The clinical personnel do not always have the time, knowledge and financial means to ensure initiation of effective treatment. Many Counties do not offer the patients the possibility of more consultations with a clinical dietician etc., and the waiting periods are often too long. Usually the treatment possibilities are better organised at the diabetes clinics, even though there can be a wait to seeing a clinical dietician and difficulty in carrying out an acceptable number of follow-up consultations.

Thus the initial treatment in particular needs to be structured better, both in relation to education of healthcare personnel and programmes for following up on patients, and in relation to the treatment possibilities that the patients are offered. This can be done by focusing on well-educated treatment teams both in general practice and in the hospital sector combined with treatment possibilities in which there is time to activate and motivate the patient to lifestyle changes. This will entail greater use of nurses and clinical dieticians in general practice.

The general practitioner should be the central therapist when it comes to non-pharmacological treatment. It should be possible to refer particularly complicated patients to a diabetes clinic for treatment. The treatment goals should be the same regardless of where the patient is followed.

The current organisation of non-pharmacological treatment in the various Danish Counties is described in Annex 7.

4.8.1 Subconclusion

- The organisation of non-pharmacological treatment in Denmark is poorly described, and often unknown.
- It is therefore recommended that the National Board of Health – in cooperation with the diabetes team’s specialist societies and the Diabetes Association – takes the initiative to systematic, well-designed, sufficiently large, coordinated and economically well-founded Danish multi-centre trials of the value of non-pharmacological treatment, including its organisation.

4.9 The patient

The treatment of Type 2 diabetes is initially based on lifestyle changes, and the involvement of the patient in treatment and control is therefore important. This self care is a fundamental principle. It is thus essential that the patient acquires the knowledge and skills necessary to be able to achieve a satisfactory level of self care. For many patients diagnosed with Type 2 diabetes, this will entail radical changes to their lifestyle, particularly in relation to diet and exercise and cessation of smoking. For many patients the changes in lifestyle will be so great that they cannot implement them – and certainly not without professional support. It is therefore important to set realistic goals and an appropriate timetable for weight loss, diet changes and exercise habits, and cessation of smoking. It is important that the diabetes team is aware that obesity is a disease that is difficult to treat.

Among certain immigrant groups there is no tradition for physical activity. Moreover, their diet is often very fat. This, together with possible language barriers, means that lifestyle changes can be difficult to implement.

Effective non-pharmacological treatment allows the patient to do without medication to a much greater extent and thereby not only avoid the economic burden that pharmacological treatment entails, but also to reduce or avoid the side effects of that treatment. A great advantage of non-pharmacological treatment is that the patients feel less ill, especially for as long as they can completely avoid pharmacological treatment. However, only the minority can presently avoid pharmacological treatment as the therapeutic goals for the Type 2 diabetes patient can only rarely be met without pharmacological treatment. In this situation it is important to underline that with effective non-pharmacological treatment it is possible to reduce both the dosage and the number of drugs needed, for example to treat raised blood pressure.

Subconclusion

- Non-pharmacological treatment will often entail such great lifestyle changes for the patient that they are very difficult to carry out (5).
- The treatment of ethnic minorities can entail special challenges in relation to their culture and a possible language barrier (5).
4.10 Economic aspects

The present health economic analysis of the non-pharmacological treatment of Type 2 diabetes is restricted to:

- Foot care and shoes for the prevention of diabetes-related foot ulcers and amputations.
- Education about diet and exercise.
- Smoking cessation.

The individual interventions are examined separately below.

4.10.1 Prevention and treatment of diabetic foot problems

No good Danish studies exist of the economic consequences of prevention and treatment of foot problems in patients with Type 2 diabetes. The assessment is therefore based on recent Swedish study (517) that utilises Markov modelling to assess the cost-effectiveness of prevention and treatment of foot problems in patients with diabetes. The Danish model is patterned on the Swedish model and has an identical structure. All data on the effectiveness of the treatment have been obtained from the Swedish model.

When reviewing the Swedish model a logical inconsistency was identified that has been adjusted in the Danish model, although without this having affected the overall conclusions of the Swedish model. Wherever possible the Danish model uses Danish data. However, it has not been possible to make good estimates of patient resource consumption in the social sector in particular, and a number of costs have therefore been directly transferred to the Danish model from the Swedish model. While this practice is not in accordance with the guidelines for economic analysis, sensitivity analyses of the cost parameters do not significantly affect the model’s conclusions.

Both the Swedish and the Danish models compare a baseline scenario (describing the existing Swedish practice) versus an alternative scenario describing the recommended practice in the Swedish study. Separate calculations are made for three age groups (persons aged 24-69 years, 70-84 years and >85 years) and for four separate risk groups:

- Risk group 1: Diabetes without any special risk factors
- Risk group 2: Diabetes combined with neuropathy
- Risk group 3: Diabetes combined with neuropathy and peripheral vascular disease and/or foot deformities
- Risk group 4: Previous foot ulcers or amputations.

The recommended practice in Sweden is that all patients receive education about foot care. Patients in risk group 2 also receive professional foot care by a podiatrist three times a year. Patients in risk group 3 receive foot care eight times a year and a pair of custom-moulded insoles for their shoes, while patients in risk group 4 receive foot care 9 times a year and one pair of shoes every 18 months.

The Markov model has been established on the basis of Swedish studies of the effectiveness of intensified treatment. Under Danish conditions the use of a Swedish baseline scenario is naturally a weakness, but the model nevertheless shows that intensification of treatment leads to both health benefits and increased costs, which is also the issue in Denmark.

Costs

In the baseline scenario in the Swedish study, 20%, 30%, 39% and 43% of the four risk groups, respectively, receive some form of podiatric care, while 5%, 8%, 16% and 34%, respectively, use preventative or therapeutic footwear. As no information is available about the services provided to the various risk groups it is assumed that for patients in risk group 1 and 2 the preventative footwear consists of custom-moulded insoles and that those patients who receive podiatric care receive it three times a year. Patients in risk groups 3 and 4 follow the Swedish guidelines with respect to both footwear and podiatric care.

Among diabetes patients who use preventative or therapeutic footwear, approx. 80% use custom-moulded shoes, while the remaining 20% make do with a pair of pre-moulded therapeutic shoes. A pair of custom-moulded orthopaedic shoes costs approx. DKK 9,000, a pair of pre-moulded therapeutic shoes approx. DKK 4,000, and a pair of insoles approx. DKK 1,000 (Skaarup Orthopaedic Shoemaker).
A consultation at a podiatrist costs approx. DKK 250. It is assumed that the yearly education consists of four consultations at a podiatrist, i.e. a total annual cost of DKK 1,000. Furthermore, it is assumed that everybody in the intervention group receives education. It is furthermore assumed that in addition to education, the patients in risk group 1 who receive intensified prevention also receive a few more services than actually recommended for this intervention group.

The costs per half-year for the specified risk groups are shown in Table 4.10.1.1. All costs are made up as half-year costs as the Markov model is based on half-yearly transition probabilities.

### TABLE 4.10.1.1
Costs (DKK) per half-year, risk groups 1-4

<table>
<thead>
<tr>
<th>Costs</th>
<th>Risk group 1</th>
<th>Risk group 2</th>
<th>Risk group 3</th>
<th>Risk group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual prevention</td>
<td>100.00</td>
<td>152.50</td>
<td>470.00</td>
<td>1,503.75</td>
</tr>
<tr>
<td>Optimal prevention</td>
<td>600.00</td>
<td>1,250.00</td>
<td>2,000.00</td>
<td>4,625.00</td>
</tr>
</tbody>
</table>

In the Swedish study, optimal prevention is set to reduce the relative risk of foot ulcers is set to 25% relative to actual prevention. This risk reduction is seen independently of age. The increased mortality among elderly people affects both the costs and the effects, however. Data on the transition probabilities are shown in the Swedish study (517).

Table 4.10.1.2 shows the half-yearly costs (over and above the prevention costs) connected with the health states encompassed by the model. These cost are a direct conversion of the Swedish costs and encompass costs in both the social sector and in the health sector as there are no Danish studies of costs in the social sector for patients with foot ulcers.

### TABLE 4.10.1.2
Half-yearly costs (DKK) for the health states encompassed by the model

<table>
<thead>
<tr>
<th>Health state</th>
<th>Cost (DKK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated foot ulcer</td>
<td>32,429</td>
</tr>
<tr>
<td>Deep foot ulcer</td>
<td>10,990</td>
</tr>
<tr>
<td>Foot ulcer and critical ischaemia</td>
<td>60,542</td>
</tr>
<tr>
<td>Costs after healing of minor amputation (under the ankle)</td>
<td>26,128</td>
</tr>
<tr>
<td>Costs after healing of major amputation (over the ankle)</td>
<td>71,722</td>
</tr>
<tr>
<td>Costs associated with the transition from deep foot ulcer to amputation</td>
<td>79,324</td>
</tr>
<tr>
<td>Costs associated with the transition from critical ischaemia to amputation</td>
<td>340,422</td>
</tr>
</tbody>
</table>

**Quality-adjusted life-years**

The model utilises English QALY values for the effect of the treatment. A weakness in the present model analysis is thus that no Danish data are included. The values used are shown in Table 4.10.1.3.

### TABLE 4.10.1.3
QALY values

<table>
<thead>
<tr>
<th>Health state</th>
<th>QALY value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No foot ulcers</td>
<td>0.80</td>
</tr>
<tr>
<td>Presence of foot ulcers (uncomplicated, deep, critical ischaemia)</td>
<td>0.44</td>
</tr>
<tr>
<td>Healed foot ulcer</td>
<td>0.60</td>
</tr>
<tr>
<td>Minor amputation</td>
<td>0.61</td>
</tr>
<tr>
<td>Major amputation</td>
<td>0.31</td>
</tr>
</tbody>
</table>

**Results of the model calculations**

The results presented in Tables 4.10.1.4 and 4.10.1.5 indicate the costs and effects for an average person receiving either existing or optimal prevention modelled over five years (10 cycles) with a discount rate of 5%. Table 4.10.1.6 indicates the costs per QALY with the given interventions.
TABLE 4.10.1.4
Costs (DKK) and effects (QALY) per average person for existing prevention

<table>
<thead>
<tr>
<th>Risk group</th>
<th>QALY</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-69 yr</td>
<td>70-84 yr</td>
<td>Over 85 yr</td>
</tr>
<tr>
<td>1</td>
<td>3.479</td>
<td>2.644</td>
</tr>
<tr>
<td>2</td>
<td>3.160</td>
<td>2.423</td>
</tr>
<tr>
<td>3</td>
<td>3.144</td>
<td>2.414</td>
</tr>
<tr>
<td>4</td>
<td>2.619</td>
<td>2.053</td>
</tr>
</tbody>
</table>

TABLE 4.10.1.5
Costs (DKK) and effects (QALY) per average person for optimal prevention

<table>
<thead>
<tr>
<th>Risk group</th>
<th>QALY</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-69 yr</td>
<td>70-84 yr</td>
<td>Over 85 yr</td>
</tr>
<tr>
<td>1</td>
<td>3,481</td>
<td>2,646</td>
</tr>
<tr>
<td>2</td>
<td>3,204</td>
<td>2,453</td>
</tr>
<tr>
<td>3</td>
<td>3,193</td>
<td>2,447</td>
</tr>
<tr>
<td>4</td>
<td>2,739</td>
<td>2,104</td>
</tr>
</tbody>
</table>

TABLE 4.10.1.6
Costs (DKK) per QALY

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Costs per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-69 yr</td>
<td>70-84 yr</td>
</tr>
<tr>
<td>1</td>
<td>1,870,062</td>
</tr>
<tr>
<td>2</td>
<td>51,421</td>
</tr>
<tr>
<td>3</td>
<td>3,142</td>
</tr>
<tr>
<td>4</td>
<td>99,781</td>
</tr>
</tbody>
</table>

From Table 4.10.1.6 it can be seen that the optimal treatment of patients in risk group 1 is hardly cost-effective, while the costs per QALY for patients in risk groups 2, 3 and 4 are negative, which means that the treatment is better and less costly. From a health economic perspective this means that the intensified treatment should be offered to patients with risk factors over and above diabetes alone.

The total costs for the groups 2, 3 and 4 are not essentially different in the two alternatives as the increased costs for prevention are virtually counterbalanced by saved treatment costs. These results are in concert with the findings of other studies.

Sensitivity analyses performed on the model calculations show that the model results – with the exception of those for patients in risk group 1 – are relatively sensitive to changes, especially in effect parameters, and hence should be interpreted with caution.

Subconclusion
- The model calculations are characterized by a number of uncertain assumptions and the cost data are mainly based on Swedish cost studies as it has not been possible to perform actual Danish studies. Moreover, the model calculations are sensitive to changes in the underlying effect variables, and one should therefore be cautious in according too much weight to them.
- Taking these reservations into account, much indicates that an intensified prevention among patient groups with a high risk of developing foot ulcers comprises good use of health service resources. The calculations concomitantly show that prevention efforts probably should not be enhanced in the case of patients without any other risk factors than diabetes.
- The costs and effects of more intensified screening and treatment of patients with foot ulcers will depend on the level at which this is presently being undertaken. The more well-functioning the existing systems, the higher the probable costs per effect unit. As the present level of examination and treatment of high-risk patients in Denmark is uncertain, among other reasons due to the considerable geographic variation, it is not possible to provide an overall estimate of the increased costs associated with intensification of treatment.
- From the overall health economic viewpoint it is hardly appropriate to offer structured prevention of foot complication to patients without other risk factors than Type 2 diabetes. Instead, the focus should
be on high-risk patients, i.e. patients in risk groups 2, 3 and 4. Most of these patients already are or have been in contact with the treatment system and actual screening is therefore unnecessary.

- Greater efforts should be made to elaborate administrative procedures to ensure that the patients are offered a prevention programme in cases where risk factors are identified.
- Actual screening of all diabetes patients will make the cost per effect unit considerably more expensive. From the health economic viewpoint, screening for foot problems among all diabetes patients is not an appropriate use of the resources.

4.10.2 Education
Diet and exercise are dealt with under the main heading education as courses and other information often deal with these themes together.

Overall, there is no evidence that the present level of education [about diet and exercise] in Denmark has any effect in the long term. Much more intensive intervention is probably needed if education and information about diet are to have long-term effects on the development of the disease. As yet, moreover, no unambiguous concept for ensuring education has yet been developed.

The amount of resources used on the education of patients with Type 2 diabetes about diet and exercise is unclear. However, based on resource use by the Steno Diabetes Center for their courses, the diet and exercise part of the course involves approx. 2½ hours of contact time with a clinical dietician/nurse per participant (regardless whether it is a group course or an individual course). Assuming that the dietician/nurse is paid DKK 200 per hour with overheads costing a corresponding amount, the part of the course concerning diet and exercise costs approx. DKK 1,000 per participant. The number of persons with Type 2 diabetes who receive education in diet and exercise nationwide is unknown. The Steno Diabetes Center receives approx. 500 new or re-referred Type 2 diabetes patients per year. If all 10,000 newly diagnosed Type 2 diabetes patients were to receive education, it would cost approx. DKK 10 million per year. On top of this is the cost of the re-referred patients.

**Subconclusion**
- Until thoroughly tested concepts have been developed for how to change exercise and dietary habits in practice, health economic considerations dictate that the existing educational programmes should not be expanded.
- Resources should instead be canalised to the development and testing of new concepts for attaining results in the long term.

4.10.3 Smoking cessation
There is no evidence pertaining to smoking cessation in diabetes patients. For risk groups, however, smoking cessation organised according to acknowledged principles is normally considered a cost-effective measure (518, 519). The cost-effectiveness ratio obtained with other smoking cessation programmes cannot be directly transferred to diabetes patients, though, as there are a number of special problems associated with smoking cessation among diabetes patients, including weight gain, that affect diabetes patients more than other persons. Conversely, the effects can be correspondingly greater in some regards for the diabetes patients as the combination of several risk factors often has a greater effect on health than the sum of the individual risk factors. Even though the cost-effectiveness of smoking cessation is unknown, it is plausible that smoking cessation in patients with Type 2 diabetes comprises a cost-effective treatment strategy.

4.11 Conclusions and recommendations

**General**
- Type 2 diabetes is a lifestyle disease.
- Weight loss due to dietary change and enhanced physical activity leads to improved regulation of glucose, blood pressure and blood lipids.
- It is uncertain how lifestyle changes should best be initiated and maintained in Type 2 diabetes.
- Lifestyle changes are often difficult to carry out and maintain.

**Diet**
- The total amount of carbohydrate is often more important for the glycaemic response than the type of carbohydrate (1b).
Sucrose does not increase the glycaemic response more than an isocaloric amount of starch and can be used as a substitute for other carbohydrates (1b).

Artificial sweeteners are safe when consumed in amounts within the recommended limits (3b).

The intake of protein does not raise the blood glucose level (1b).

Patients with Type 2 diabetes can consume normal amounts of protein unless the renal function is affected (4).

A diet with a low fat content contributes to a minor weight loss (1b).

Fat intake has to be restricted if weight loss and reduction in LDL cholesterol are desired (1a).

Good glycaemic regulation only has a moderate effect on diabetic dyslipidaemia (1b).

Despite the many studies undertaken there is no evidence that the intake of antioxidants over and above that present in the diet has any beneficial effects (1b).

The consumption of moderate amounts of alcohol together with food does not influence the blood glucose level (1b).

Weight loss

Structured lifestyle programmes encompassing dietary changes with reduced energy and fat intake in combination with increased exercise together with frequent patient contact can lead to a weight loss of 5-10% of the initial weight (1a).

Weight loss of only 5% improves the regulation of blood glucose, blood pressure and blood lipids (1b).

If normalization of glucose is the therapeutic goal, the weight loss required is often so great as to be unrealistic for the patient (1a).

The use of very low calorie diet (VLCD) can lead to more rapid weight loss, but the long-term results are no better than with conventional dietary treatment (1b).

Surgical treatment of extreme overweight in Type 2 diabetes entails large and persistent weight losses and hence often leads to remission of the diabetes (3b).

Non-pharmacological treatment of raised blood pressure, dyslipidaemia and nephropathy

Reduced salt intake (<6 g daily) and weight loss lead to a fall in blood pressure (1a).

For patients with diabetic dyslipidaemia, improvement in glycaemic regulation, weight loss, enhanced physical activity and reduced the intake of saturated fat have a positive effect on the lipid profile in the blood (2b).

Protein restriction to 0.8-1.0 g per kg body weight in patients with microalbuminuria and to 0.8 g per kg body weight in patients with nephropathy reduces the progression of nephropathy (1b).

Self-monitoring of blood glucose

There is no evidence that self-monitoring of blood glucose as an isolated treatment intervention has any general effect (1a).

If the patient is undergoing insulin treatment and adjusts the insulin dose himself, self-monitoring of blood glucose does have an effect (4).

If self-monitoring of blood glucose is to have an effect, a minimum requirement is that this treatment modality is integrated with the other non-pharmacological self care behaviour (5).

Self-monitoring of blood glucose is a useful tool in relation to self care as it shows the patient how the diabetes reacts to changes, for example in diet and exercise. The results can also help motivate lifestyle changes (5).

Exercise

Exercise improves glycaemic regulation (1a).

Exercise improves the lipid profile in the blood (1b).

Exercise helps maintain a weight loss (1a).

Smoking

Smoking exacerbates the late diabetic complications (1b).

Diabetes patients seem to accord low priority to smoking cessation, partly because of the risk of weight gain (2b) and the development of depression (3a).

Education

The effect of education on glycaemic regulation, lipid status and hypertension is limited (1b).

Education has effects on knowledge about diabetes and practical skills, e.g. measurement of blood glucose (1b).
Education has little or no effect on weight in the long term (1b).

The effect of education diminishes with time following cessation of education (1b).

It is not possible to identify which forms of education or educational programmes yield the best results, although contact time and the number of contacts seem to be of decisive significance for the effect (1a).

There is a need for more research on how to enhance the beneficial effects of education (5).

**Shared care**

- Shared care between the primary sector and the diabetes outpatient clinics is a method of structuring diabetes treatment with respect to screening for diabetes, referral, treatment, screening for late diabetic complications and the communication between the primary and secondary sectors.
- Shared care has only been established in a few counties in Denmark.
- How best to implement shared care is presently unclear.

**The diabetic foot**

- The patient's knowledge about foot care is temporarily enhanced by education (1b).
- In patients at risk, education reduces the frequency of ulcers, amputations and the callus formation (1b).
- The amputation rate is 4-5-fold higher in patients that are not regularly examined by a podiatrist (2b).
- Multidisciplinary treatment considerably reduces the frequency of leg amputation (1a).

**Organisation**

- The organisation of non-pharmacological treatment in Denmark is poorly described and often unknown, it often differs between hospitals and general practice, and also varies within the same County.
- Increased cooperation between the primary and the secondary sectors could be an opportunity to strengthen non-pharmacological treatment, e.g. via diabetes schools and shared care (5).
- Enhanced education of healthcare personnel and a higher degree of utilisation of nurses, podiatrists and clinical dieticians in non-pharmacological treatment could help improve non-pharmacological treatment (5).
- At present there is no clear description of which organisation best induces lifestyle changes.
- Effective non-pharmacological treatment requires frequent and lifelong contact between patient and healthcare professional (5).
- There is a great need for research to elucidate how effective non-pharmacological treatment can be implemented (5).

**The patient**

- For many patients, lifestyle changes will entail a radical reorganisation of their lives and will therefore difficult to implement (5).
- Many patients will be unable to implement lifestyle changes without professional support (5).
- A barrier to effective non-pharmacological treatment can lie with the healthcare professional due to lacking faith in its efficacy (5).
- Ethnical minorities can pose special challenges in relation to non-pharmacological treatment due to their culture and a possible language barrier (5).

**Economy**

**Foot care**

- There is much to indicate that intensified preventative efforts in patient groups at high risk of developing foot ulcers constitutes good utilisation of health service resources. Furthermore, the calculations show that efforts should probably not be enhanced in the case of patients without risk factors other than diabetes.

**Education**

- Even though it is well documented that diet and exercise affect Type 2 diabetes, there is far greater disagreement about how people can be made to change their lifestyle in practice. Before thoroughly tested concepts have been developed for how exercise and dietary habits can be changed in practice, health economic considerations dictate that the existing educational programmes should not be expanded.
- Resources should instead be canalised to the development and testing of new concepts for attaining results in the long term.
Smoking cessation

Even though the costs associated with smoking cessation are unknown, it is plausible that smoking cessation among patients with Type 2 diabetes is a cost-effective treatment strategy.

General recommendations

Recommendations concerning non-pharmacological treatment of Type 2 diabetes are difficult to make because although Type 2 diabetes is considered a lifestyle disease, the evidence for the permanent value of lifestyle changes (dietary changes, weight loss, exercise, smoking cessation), education and self-monitoring of blood glucose is sparse. There is thus less certainty about the effects of non-pharmacological intervention than of pharmacological treatment with regard to cardiovascular disease, diabetic nephropathy, diabetic retinopathy and mortality. It should be noted, though, that the pharmacological intervention studies available are based on concomitant non-pharmacological treatment. Conversely, for ethical reasons it cannot be expected that scientific studies of the value of non-pharmacological treatment can be initiated without pharmacological intervention also being permitted.

It is thus recommended that low-fat diet, weight loss, regular exercise and smoking cessation should comprise the foundation of all treatment of Type 2 diabetes, and that self-monitoring of blood glucose should be integrated with the remaining non-pharmacological self care behaviour (A).

The expected long-term value of education, including education in diabetes schools, has not been documented, but is on the other hand the foundation for the non-pharmacological treatment, which in itself is the foundation for the pharmacological treatment. It is therefore recommended that education should be offered to all patients with Type 2 diabetes. Before considering changing the current educational practices (which are poorly described), for example through the establishment of more diabetes schools, experience with the activities at the existing diabetes schools should be carefully evaluated (D).

Specific recommendations

A hypocaloric, low-fat diet is recommended for overweight Type 2 diabetes patients (A).

The diabetic diet should consist of 50-60 E% carbohydrate, 20-30 E% fat and 10-20 E% protein (D).

Carbohydrates and monounsaturated fat should together comprise 60-70 E% (D).

Maximally 10% of the energy intake should derive from saturated fat and transfat (A).

It is recommended that cholesterol intake should be less than 300 mg daily (A).

A high fibre content diet is recommended, but Type 2 patients should not consume more fibre than persons without diabetes (D).

The usual dietary recommendations for the intake of minerals and vitamins also apply to Type 2 diabetes patients (A).

The usual recommendations concerning alcohol intake also apply to patients with Type 2 diabetes (A).

It is recommended that patients with microalbuminuria reduce their daily intake of protein to <1.0 g/kg body weight (0.8 g/kg for patients with macroalbuminuria) (A).

It is recommended that patients with raised blood pressure reduce their daily salt intake to <6 g (A).

It is recommended that all Type 2 diabetes patients be taught self-monitoring of blood glucose in accordance with their individual needs (C).

It is recommended that all Type 2 diabetes patients perform regular physical activity (A).

Smoking cessation should be accorded high priority in the treatment of Type 2 diabetes (A).

Regular podiatric care, education of patients at risk and the use of special therapeutic shoes and custom-moulded insoles are recommended as these measures can reduce the frequency of foot ulcers and amputations (A).

Education in lifestyle changes is the foundation for treatment of Type 2 diabetes (A).

It is recommended that standards be developed for the content of educational programmes (D).

Education in self care should be offered to diabetes patients at the time of diagnosis and regularly thereafter so that they understand the importance of regular checkups for the late complications of diabetes (A).

In practical terms, increasing the focus on non-pharmacological treatment will necessitate expansion of the dietician service in the primary sector, the use of nurses and the education of healthcare workers (D).
5 Pharmacological treatment of Type 2 diabetes

When a person is diagnosed as having diabetes it becomes apparent that the high blood glucose values and the associated symptoms are rarely the only problem to be solved. Overweight is a contributory cause of diabetes in approx. 85% of patients, and more than 60% have either raised blood pressure (hypertension), disturbances of fat metabolism (dyslipidemia) or both. Diabetes is thereby part of the so-called metabolic syndrome. The elements of this metabolic syndrome often develop before the person has got diabetes, and progresses in a long asymptomatic phase with undetected diabetes. Together with the other so-called risk factors – hereditary susceptibility towards cardiovascular disease, male gender, smoking and physical inactivity – these individually and especially in combination enhance the risk of early atherosclerosis in the heart and vessels. This is probably why approx. 20% of the patients have developed cardiovascular disease by the time Type 2 diabetes is detected.

Pharmacological treatment refers to treatment with drugs such as tablets that lower blood glucose. Polypharmacological treatment refers to a combination treatment with several different types of drugs that are not solely directed at treatment of the high blood glucose, but also treat other identified risk factors and states that enhance the risk of cardiovascular disease. This applies, for example, to raised blood pressure and changes in blood lipids. Intensive polypharmacological treatment refers to efforts to treat all identified risk factors in accordance with the criteria and with the drugs for which scientific evidence has been found in trials in which the drug has been tested in monotherapy.

<p>| TABLE 5.0.1 |</p>
<table>
<thead>
<tr>
<th>Aim of supplementing lifestyle intervention with pharmacological or polypharmacological treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>- <strong>Eliminate/ alleviate symptoms</strong></td>
</tr>
<tr>
<td>- Prevent the development/ progression of late diabetic complications:</td>
</tr>
<tr>
<td>- Cardiovascular disease: coronary atherosclerosis (chest pain, thrombosis and heart failure), leg vessels (foot ulceration, gangrene, amputation).</td>
</tr>
<tr>
<td>- Diabetic changes to the small blood vessels (microvascular disease): retinopathy (partial sightedness, blindness), nephropathy (albuminuria, renal failure), neuropathy (loss of peripheral sensation, foot ulceration).</td>
</tr>
<tr>
<td>- Reduce the enhanced mortality</td>
</tr>
</tbody>
</table>

If a change in lifestyle through dietary change and enhanced exercise (see previously) is unable to sufficiently reduce the diabetic patient’s symptoms, pharmacological treatment is indicated. If the diabetes patient concomitantly has cardiovascular disease or there is a major risk of this, intensive polypharmacological treatment is indicated.

As is apparent from Section 5.4 and Figure 5.4.1 and 5.4.2, polypharmacological treatment is a reality in Denmark. Thus just under 8% of all Type 2 diabetes patients in Aarhus County are treated with both hypoglycaemic agents, antihypertensive drugs and lipid-lowering drugs. This percentage is considered to be too low in that just under 50% of the patients have cardiovascular disease or are in the high risk category and therefore meet the indication for concomitant treatment with the three above-mention types of drugs in accordance with current clinical guidelines and guidance reports (2). Considering solely treatment with hypoglycaemic agents, figures from Vejle County show that 27% of the patients had not had their glycosylated haemoglobin measured in 1997 and that of those in whom it had been measured, regulation was good in 15%, acceptable in 20% and poor in 65% (520, 521). At the same time, 29% of the patients were treated with dietary intervention alone, 54% received hypoglycaemic tablets and 17% received insulin. These figures show the treatment is suboptimal relative to the current recommendations. In this connection it is important to note that even with well carried out scientific studies the quality of treatment rarely fully complies with the goals set by the studies. The reason that treatment quality does not live up to the recommendations is unclear, as will become apparent from the sections on the patient perspective and organisation of treatment.

This chapter of the report examines the four main elements of health technology assessment – the technology, the patient, the organisation and the economic aspects – in relationship to each of the pharmacological treatment principles that have an effect on overweight in Type 2 diabetes, have an effect on blood glucose, blood pressure and blood lipids or reduces the risk of cardiovascular disease (see below). Finally, polypharmacological treatment is examined.

A comprehensive assessment of a pharmacological treatment must also include information on how much of the recommended medicine the diabetes patient can be expected to have to take (compliance) and the
disadvantages on the treatment such as *side effects* and *interactions*. In the present context, interactions are understood to mean changes in the effects of the individual treatments if they are administered in combination. These aspects will be discussed in the section on the section entitled “The patient”.

**TABLE 5.0.2**
Principles of pharmacological treatment

| – Pharmacological treatment of overweight in Type 2 diabetes |
| – Treatment of hyperglycaemia (hypoglycaemic agents) |
| – Treatment of hypertension (antihypertensive drugs) |
| – Treatment of dyslipidaemia (lipid-lowering drugs) |
| – Treatment of micro- and macroalbuminuria |
| – Other pharmacological treatment with a prophylactic effect on the development and/or progression of manifest cardiovascular disease (ACE inhibitors and acetylsalicylic acid (aspirin)). |

5.1 The technology

The effect of the pharmacological treatments is best determined by means of randomised clinical trials (RCTs) that determine how many persons experience an event (for example coronary thrombosis or renal failure) among those receiving active medication (the treatment group) compared with those receiving inactive placebo (the control group).

Based on this type of study it is possible to express the risk of an event and the possible treatment effect in different ways, as explained below. These terms are used in the tables in the present chapter.

- **Risk**, expressed as the likelihood that a person will experience an particular event (e.g. a coronary thrombosis) during the course of a specified period of time. In the present report the risk is expressed as the number of events per 100 observation years. *Example*: 15 persons in a group of 100 persons develop a coronary thrombosis during a 5-year period. The risk is (event/total patient years) × 100, i.e. 15/(100×5)×100=3 per 100 patient years.

- **Absolute risk reduction** is the difference between the risk in the group receiving placebo and that in the group receiving the active treatment. *Example*: If the risk with placebo is 5 events per 100 patient-years and the risk with treatment is 3 events per 100 patient-years, then the absolute risk reduction is 5–3=2 events per 100 patient-years.

- **Relative risk reduction** is the risk reduction with active treatment expressed as a percentage of the risk in the control group. *Example*: the absolute risk reduction is 2, and the absolute risk reduction in the control group is 5 per 100 patient-years. The relative risk reduction is (2/5)×100%=40%.

- **Number needed to treat** (NNT) is a measure of the magnitude of the effect of active treatment when a group of persons are treated. NNT is defined in this report as the average number of persons who have to be treated for a given time of prevent the occurrence of a single event. *Example*: The absolute risk reduction is 2 events per 100 patient-years. If one selects a 10-year observation period the treatment will prevent 0.2 events per 10 patient years, i.e. 1/0.2=5 persons have to be treated for 10 years to prevent a single event, i.e. NNT=5.

- **Treatment efficacy in the individual patient** is not something that can be determined from the risk reduction or the NNT. These figures provide information about the ability of the treatment to reduce the number of events in a group of persons with the same disease, but nothing about the individual’s chances of avoiding the event. They thus only reflect the average risk reduction.

In the present report we have chosen to express treatment efficacy in terms of the **10-yr NNT** except for drugs with renoprotective effects in Section 5.1.5 and Table 5.1.5.1, where we use the 3-yr NNT. If the course of the disease or treatment efficacy change with time, the use of the 10-yr NNT can yield uncertain results if one extrapolates from studies of shorter duration.

**Reservations regarding the results of randomised clinical trials**

Randomised clinical trials showing the effect of a given treatment are not always available, and in other cases – as in this part of the report – various aspects of the studies give cause for criticism. The seriousness of the criticism determines whether reservation must be expressed about the results or conclusions of a given study or whether it has to be completely excluded as scientific evidence. If there are serious reservations about the results of a study this is indicated by the letter “F” in the evidence grade.
Due to the nature of the treatment, a blinded comparison of active treatment and placebo is not always possible, and it is often considered unethical to give the control group inactive placebo. The majority of modern controlled trials thus test different forms of treatment against each other, for example a new drug versus one or more drugs already in use. Alternatively, the new drug or placebo is administered on top of the existing treatment. By achieving the same treatment effect – for example lowering of blood glucose or blood pressure – in the various treatment groups it is possible to determine whether the new treatment is advantageous or disadvantageous compared with the old treatment.

For the same reason – if for example blood glucose or blood pressure becomes too high during a trial – it is nearly always necessary to supplement the treatment with other drugs. What one therefore ends up comparing is various combinations of drugs in which the two drugs being investigation comprise the basic treatment.

Most trials of antihypertensive and lipid-lowering treatment have been performed on large groups of persons of whom less than 10% were diabetics. Investigation of the effect in diabetes patients was rarely one of the prior aims of these subgroup studies. Apart from an inadequate number of subjects the criteria for the diabetes diagnosis have not been set at the start of the study or no effort has been made to differentiate between patients with and without diabetes by means of fasting blood glucose or oral glucose tolerance. Most often the group is defined as “known” diabetes patients. With studies of patients with hypertension one can expect that approx. 5% – over and above the known cases – can have undetected diabetes. For these reasons the results of such subgroup analyses should be interpreted with caution. In the tables comparing the studies the subgroup studies are indicated by the letter “S” as opposed to a “P” for primary analysis.

Another related problem is the stressing of “chance observations” or secondary results when the primary aim of the study has been something else. If this is the case, it is either indicated in the tables or elaborated in the text. The same applies to other reservations about the controlled studies.

In the section on treatment of hyperglycaemia we have supplemented the results of the available randomised trials with results that have previously been analysed as observation studies. Here the obtained treatment effect on blood glucose is compared with the effect on the occurrence of late complications. This does not allow calculation of the risk reduction or NNT with active treatment, but solely enables statement of whether a given difference in the attained blood glucose level is accompanied by a given difference in the occurrence of late complications.

5.1.1 Pharmacological treatment of obesity in Type 2 diabetes

As mentioned in Chapter 4, one of the goals of the non-pharmacological treatment of the overweight Type 2 diabetes patient is to obtain a weight loss. Despite intensive dietary instruction and advice on exercise the weight loss achieved is often insufficient and cannot be maintained. The purpose of supplementary pharmacological treatment of overweight is to increase the number patients who maintain a major weight loss over time. The precondition for considering pharmacological treatment is partly severe overweight and partly an insufficient effect of continuous non-pharmacological treatment. In Denmark, two drugs are approved for treatment of overweight – sibutramine and orlistat. None of these have been shown to have any effect on late complications, including cardiovascular disease in Type 2 diabetes. Thus only their effect on overweight and risk factors is examined below.

**Sibutramine**

Sibutramine acts by reducing the appetite and increasing the metabolism. The effect of sibutramine treatment of overweight Type 2 diabetes patients compared to placebo has been investigated in six randomised trials (522-527) (1b). In all cases the treatment was given as a supplement to instruction in slimming diet (hypocaloric diet). After 3-12 months there was a 2-9 kg greater weight loss with sibutramine than with placebo. The effect was seen both in patients treated with diet alone and in patients treated with diet and hypoglycaemic drugs (sulfonylurea and metformin).

The effect of sibutramine with or without concomitant lifestyle changes has been elucidated in one single randomised trial. Instruction in hypocaloric diet and advice on 30-40 minutes of physical exercise 4-5 times per week in combination with sibutramine compared with sibutramine alone resulted in a two-fold greater weight loss in the course of 1 year – 11% as opposed to 4.2% (528) (1b).

A statistically significant fall in the blood glucose and blood lipids was only seen in patients who achieved a marked weight loss with sibutramine (526, 527) (1b).
Compared with placebo, treatment with sibutramine was more frequently accompanied by an increase in diastolic blood pressure, except among patients with a great (>10%) weight loss (526, 527) (1b).

**Orlistat**

Orlistat inhibits pancreatic lipase with the result that approx. 30% of the fat consumed is not absorbed from the gut. Fat food will therefore cause diarrhoea.

The effect of orlistat in Type 2 diabetes has been examined in randomised trials of overweight patients treated with different types of hypoglycaemic drugs (see below) and hypocaloric, low-fat diet (366, 529-531) (1b). Twelve months of orlistat treatment resulted in a 1½-3-fold greater weight loss than with placebo, and 2-3-fold more patients lost more than 5% of their weight. Moreover, the reduction in waist girth was doubled. The greatest absolute weight loss (6.2% versus 4.3%) was seen in the study of sulfonylurea-treated patients (366, 529) (1b), while the loss was smallest in the study of insulin-treated patients (3.8% versus 1.2%) (531) (1b). In all the studies there was a modest, but statistically significant beneficial effect on the blood glucose level despite the reduction being greater with the hypoglycaemic agents. A meta-analysis of 1,249 orlistat treated versus 1,230 placebo treated overweight patients, of which a number were diabetes patients, showed that HbA1c was an average of 0.45 percentage points lower. Among the patients with the poorest glycaemic regulation, HbA1c was 1 percentage point lower (532) (1a).

All studies revealed a beneficial effect on blood lipids (decreasing LDL cholesterol and triglyceride together with an increasing HDL cholesterol) in all overweight subjects (533) (1b). A beneficial effect is also seen on blood pressure.

Even though the intake of a fatty diet entails loose stools during treatment with orlistat, the drop-out rate among the orlistat-treated groups is not greater – to the contrary in fact (530) (1b). Conversely, the otherwise harmless side effects can be used to promote healthy dietary habits (367) (1b).

If orlistat has not had an effect on weight or HbA1c after 3 months, no effect of long-term treatment can be expected, and treatment should therefore be terminated (534) (1b).

**Subconclusion**

- No long-term data is available concerning the pharmacological treatment of overweight in Type-2 diabetes patients (>2 years).
- Treatment with orlistat (1a) or sibutramine (1b) combined with a hypocaloric diet results in a significantly greater weight loss than with placebo. The effect is moderate.
- Weight loss in connection with orlistat treatment has beneficial effects on the blood glucose level, improves the lipid profile and reduces the blood pressure (1a).
- Orlistat treatment is associated with increased occurrence of gastrointestinal side effects compared with placebo (1b).
- Sibutramine has no effect on the blood glucose level compared with placebo (1b).
- Sibutramine can be associated with an increase in blood pressure (1b).

**Recommendation**

Pharmacological treatment of overweight in Type 2 diabetes cannot generally be recommended. The studies undertaken are too short, and the possible effect on late complications and mortality is unknown.

### 5.1.2 Pharmacological treatment of hyperglycaemia

The aim of dietary change and exercise and – in case this is insufficient – pharmacological treatment with tablets and/or insulin is to lower the blood glucose level towards normal.

**TABLE 5.1.2.1**

<table>
<thead>
<tr>
<th>Drugs with hypoglycaemic effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
</tr>
<tr>
<td>Repaglinide/nateglinid (sulfonylurea like effect)</td>
</tr>
<tr>
<td>Acarbose</td>
</tr>
<tr>
<td>Metformin</td>
</tr>
<tr>
<td>Thiazolidinediones (glitazones)</td>
</tr>
<tr>
<td>Insulin</td>
</tr>
</tbody>
</table>
Until recently there were three pharmacologically different types of tablets, of which only two, sulfonylurea substances and metformin, have been used in studies mentioned in this part of the report. New classes of drugs have now appeared on the market (glitazones and repaglinid and nateglinid). They have a well-documented effect on blood glucose and can therefore be presumed to have a corresponding effect on late complications in the small vessels. The glitazones have a favourable effect on the ability of the Type 2 diabetes patient to utilise his own insulin and on blood lipids. Their possible effect on the risk of cardiovascular disease is presently being investigated. The place of these new drugs in pharmacological treatment therefore remain to be fully clarified.

What is the significance of a reduction in the blood glucose level with the drugs mentioned for the Type 2 diabetes patient as regards possible symptoms, the risk of developing late complications and mortality? In the following the scientific studies that shed light on these questions will be reviewed.

**Does hypoglycaemic treatment have an effect on the symptoms of Type 2 diabetes?**

The most common symptoms of raised blood glucose are frequent urination, increased thirst, weight loss and fatigue. Fifty percent of the patients have no symptoms at the time of diagnosis, though (535) (2b). It is a common clinical experience, but also demonstrated scientifically (536) (2b), that treatment of Type 2 diabetes with dietary change, weight loss and hypoglycaemic agents removes or alleviates possible symptoms.

**Does hypoglycaemic treatment have any effect on the development and progression of late complications in the small vessels (eyes, kidneys and peripheral nerves), and are some treatment principles advantageous as compared with others?**

Long-term observation studies of Type 2 diabetes patients have shown a statistically significant correlation between a high blood glucose level measured by means of HbA1c and an increased occurrence of late complications in the small vessels (eyes, kidneys and peripheral nerves) (537, 538) (2b). The issue has been addressed more closely in two RCTs, the United Kingdom Prospective Diabetes Study (UKPDS) (383) (1b) (539) (1b(F)) and the Kumamoto Study (540) (1b).

**UKPDS**

In the UKPDS, 4,207 patients with newly diagnosed Type 2 diabetes were randomised to treatment either with primarily dietary change and a treatment goal of a fasting blood glucose of less than 15 mmol/l (“conventional treatment”) or primarily intensive treatment with either insulin, sulfonylurea or metformin with a treatment goal of a fasting blood glucose of 6 mmol/l or less. The patients were followed for an average of 10 years during which it was necessary to initiate treatment or supplement the primary treatment with tablets or insulin in order to meet the treatment goal. At the end of the study the treatment groups were compared according to which primary treatment they had received even though the patients had often had several drugs, especially those in the intensively treated group. For example, 60% of the patients randomised to intensive treatment with sulfonylurea had either switched to insulin or been given supplementary metformin during the last half of the study due to increasing blood glucose (539) (1b(F)).

Intensive and conventional treatment were compared to determine the significance of the blood glucose level for the occurrence of primarily “all diabetes related events”, “diabetes related mortality” and “general mortality” (Table 5.1.2.2) and secondarily “coronary thrombosis”, “cerebral infarct”, “amputations and mortality due to impaired circulation” as well as “microvascular late complications”. “All diabetes related events” encompassed all diabetes-related deaths and all late complication in the small and large vessels.

The difference in blood glucose level between intensively and conventionally treated patients was modest – HbA1c 7% versus 7.9%, respectively, which corresponds to a difference of approx. 1.5 mmol/l in average blood glucose over the 10 years of observation (383) (1b).

Intensive treatment with metformin was only given to overweight patients, and the comparison with conventionally treated overweight patients and with the sulfonylurea- and insulin treated overweight patients was therefore published separately. In this part of the study the difference in blood glucose level between intensively metformin treated and conventionally treated overweight patients was even smaller – HbA1c 7.4% versus 8.0% (539) (1b(F)).

Intensive treatment with sulfonylurea or insulin reduced the risk of “diabetes-related events” (Table 5.1.2.2). This includes development or progression of “microvascular late complications”, where the risk reduction per 100 patient-years was 0.28, corresponding to a NNT of 36 (383) (1b(F)).
If the effect of nine years of intensive treatment on the late complications is evaluated as the development or progression of diabetic changes in the eyes, the development of microalbuminuria (expression of incipient renal disease) or an affect on peripheral nerves – i.e. in a more uncertain and subjective manner a statistically significant reduction is found, namely 0.65 per 100 patient-years for retinopathy, 0.62 per 100 patient-years for microalbuminuria and 0.44 per 100 patient-years for peripheral neuropathy (383) (2b(F)).

The effect of intensive sulfonylurea-based and insulin-based treatment was comparable as regards these primary and secondary events (383) (1b).

Analysing the UKPDS as an observation study (541) (2b) in which the average blood glucose achieved and the occurrence of late complications are compared irrespective of the treatment given yields a relative risk reduction of 37% per 1 percentage point lower HbA1c. The study also revealed that the relationship between the blood glucose level (HbA1c) and the appearance or progression of microvascular disease seems to be exponential with a modest risk when HbA1c is below 6.5-7.0% and a continuously increasing risk when HbA1c is over 8.5-9.0%.

Only 9% of the primarily diet-treated Type 2 diabetes patients in the UKPDS were able to maintain a satisfactory blood glucose level (HbA1c ≤7%) after nine years of observation. For the primarily sulfonylurea-treated patients the corresponding figure was 24%, while that for the primarily insulin-treated patients was 28% and that for the primarily metformin treated patients was 13% (322) (2b). Combination treatment with several drugs was thus well justified in approx. 65% of the patients just nine years after the onset of the disease. The need to supplement sulfonylurea treatment with insulin in order to obtain a satisfactory response has been demonstrated in a recent analysis of the results of the UKPDS (542) (1b(F)). This shows that 15% of Type 2 diabetes patients should be given insulin within the first year, and 50% within the first five years, if the blood glucose level is to be optimal.

The UKPDS Study was non-blind, the study was continued beyond the planned period of time due to lack of effect at the planned evaluation time, only 15 out of 23 centres participated in the metformin study, and many patients in both the intensively and conventionally treated group were being treated with the same combinations of drugs at the end of the study (539) (2b) (543) (5). Moreover, it has been criticised that the reduction in the risk of ‘microvascular late complications’ was mainly based on a reduction in laser treatment of retinopathy and not in blindness or renal failure (543) (5). Finally, the metformin study was not planned from the start.

The Kumamoto Study

This Japanese study encompassed 110 lean Type 2 diabetes patients who were randomised to as intensive insulin treatment as possible (‘multiple injections’) or usual insulin treatment (540) (1b(F)). The development and progression of late complications in eyes and kidneys were followed for six years. In average a significant difference in HbA1c was obtained – 7.1% versus 9.4% – corresponding to a difference of 3-4 mmol/l in blood glucose level. As is apparent from Table 5.1.2.2 intensive insulin treatment resulted in a significant risk reduction. Only 2-3 patients have to be treated intensively for 10 years in order to avoid the development or progression of microvascular late complications in the eyes and kidneys in a single patient.

The Kumamoto Study is less relevant for Danish conditions than the UKPDS study as these lean Japanese represent a special type of insulin-treated Type 2 diabetes that is uncommon in Denmark and elsewhere in Europe.

Does hypoglycaemic treatment affect mortality and the development of late complications in the large vessels and heart (cardiovascular disease)?

The risk of development of cardiovascular disease increases with increasing blood glucose even prior to the development of manifest diabetes. At the same time the occurrence of other risk factors for cardiovascular disease increases (544) (2b). In the group of patients with “impaired glucose tolerance” the relative risk of death is increased by approx. 50% (12) (2b). The relationship between the risk of cardiovascular disease and blood glucose level is less clear once the disease has developed. Two large Finnish observation studies show a weak, but statistically significant relationship between HbA1c and the occurrence of cardiovascular disease (545) (2b).

As is apparent from Table 5.1.2.2, intensive treatment with insulin or sulfonylurea in the UKPDS did not result in a statistically significant reduction or increase in mortality. There was a clear tendency towards a
reduction in the risk of coronary thrombosis (0.27 per 100 patient-year). There was no reduction in the risk of stroke or amputations. It made no difference whether the primary treatment was insulin or sulfonylurea. Previous suspicion that sulfonylurea and insulin might increase the risk of cardiovascular disease (546) (1b) thus could not be substantiated.

Analysing the occurrence of cardiovascular disease among all patients irrespective of the treatment given but in relationship to the blood glucose level achieved reveals a statistically significant relative risk reduction of 14% for coronary thrombosis for each percentage point decrease in HbA1c (541) (2b).

An intensive treatment strategy with metformin to overweight Type 2 diabetes patients compared with a conventional strategy reduced the risk of “general mortality” and “diabetes related mortality” (Table 5.1.2.2), but also of “coronary thrombosis” (0.7 per 100 patient-years, NNT 14.3).

This effect of metformin treatment on the risk of cardiovascular disease has subsequently been discussed, partly as it must be considered as a subgroup analysis and partly because the difference in blood glucose level achieved in the two groups was modest. Moreover, mortality was found to be higher in a small group of patients who received intensive sulfonylurea treatment supplemented with metformin late in the study (539) (1b(F)) than in a group that continued with sulfonylurea. These groups were very small and not directly comparable, however.

It is generally accepted, though, that metformin has a positive effect on the risk of cardiovascular disease, and that this effect probably is probably additional or parallel to the hypoglycaemic effect (543) (5).

In the Kumamoto study there was no difference in mortality or occurrence of cardiovascular disease (540) (1b).

**Drawbacks of intensive hypoglycaemic treatment**

Intensive blood glucose control with insulin and sulfonylurea is accompanied by an enhanced risk of serious hypoglycaemic attacks (383) (2b). Given a comparable average blood glucose concentration the risk was approx. 10-fold less than in Type 1 diabetes, however (547) (2b).

Compared with “conventional” hypoglycaemic treatment, intensive insulin or sulfonylurea treatment was accompanied by an average weight increase of 3.1 kg over 10 years (greatest for insulin), while there was no major weight increase among the metformin-treated patients (383, 539) (2b).

**TABLE 5.1.2.2**

**Randomised trials of the value of glycaemic control**

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary or Subgroup analysis</th>
<th>No. of patients at start of project</th>
<th>Duration of follow-up period (yr)</th>
<th>Outcome measure (only the primary outcome measure is stated)</th>
<th>Risk: Events per 100 patient-years</th>
<th>Absolute risk reduction per 100 patient-years</th>
<th>Relative risk reduction %</th>
<th>P-value</th>
<th>Number needed to treat, NNT per 10 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS – all (intensive vs. conventional treatment)</td>
<td>P</td>
<td>3,867</td>
<td>10.0</td>
<td>All diabetes related events</td>
<td>4.09</td>
<td>4.60</td>
<td>0.51</td>
<td>11</td>
<td>0.029</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diabetes related mortality</td>
<td>1.04</td>
<td>1.15</td>
<td>0.11</td>
<td>10</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>General mortality</td>
<td>1.79</td>
<td>1.89</td>
<td>0.10</td>
<td>5</td>
<td>0.44</td>
</tr>
<tr>
<td>UKPDS - overweight (metformin- vs. conventional treatment)</td>
<td>S</td>
<td>753</td>
<td>10.7</td>
<td>All diabetes related events</td>
<td>2.98</td>
<td>4.33</td>
<td>1.35</td>
<td>31</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diabetes related mortality</td>
<td>0.75</td>
<td>1.27</td>
<td>0.52</td>
<td>41</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>General mortality</td>
<td>1.35</td>
<td>2.06</td>
<td>0.71</td>
<td>34</td>
<td>0.011</td>
</tr>
<tr>
<td>UKPDS - overweight (other intensive vs. conventional treatment)</td>
<td>S</td>
<td>1,293</td>
<td>10.7</td>
<td>All diabetes related events</td>
<td>4.01</td>
<td>4.33</td>
<td>0.32</td>
<td>7</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diabetes related mortality</td>
<td>1.03</td>
<td>2.27</td>
<td>0.24</td>
<td>19</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>General mortality</td>
<td>1.89</td>
<td>2.06</td>
<td>0.17</td>
<td>8</td>
<td>0.49</td>
</tr>
<tr>
<td>Kumamoto study (primary prevention)</td>
<td>P</td>
<td>55</td>
<td>8</td>
<td>Diabetic retinopathy</td>
<td>1.9</td>
<td>6.0</td>
<td>4.1</td>
<td>68</td>
<td>0.022</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Microalbuminuria)</td>
<td>1.4</td>
<td>5.4</td>
<td>4.0</td>
<td>74</td>
<td>0.029</td>
</tr>
<tr>
<td>Kumamoto study (secondary prevention)</td>
<td>P</td>
<td>55</td>
<td>8</td>
<td>Diabetic retinopathy</td>
<td>3.0</td>
<td>7.0</td>
<td>4.0</td>
<td>57</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Microalbuminuria)</td>
<td>2.0</td>
<td>5.0</td>
<td>3.0</td>
<td>60</td>
<td>0.043</td>
</tr>
</tbody>
</table>

**Subconclusion**

Intensive hypoglycaemic treatment reduces the risk of late diabetic complications such as retinopathy, nephropathy and neuropathy in Type 2 diabetes (1b). It is recommended that Type 2 diabetes patients are offered intensive hypoglycaemic treatment aimed at reducing HbA1c to less than 7%.
The relationship between the blood glucose level achieved and the risk of microvascular late complications is exponential, with a greater risk the higher the blood glucose level (2b).

Intensive hypoglycaemic treatment based on sulfonylurea or insulin neither increases nor decreases the risk of death or cardiovascular disease (1b).

The effect on late complications of intensive hypoglycaemic treatment based on sulfonylurea with supplementary insulin treatment on demand is no different from that of insulin treatment alone (1b).

With overweight patients, intensive hypoglycaemic treatment based on metformin seems to reduce mortality and the risk of coronary thrombosis. This treatment is also associated with a lower risk of hypoglycaemia and weight gain (1b).

Treatment with several different hypoglycaemic agents often becomes necessary during the first 10 years after Type 2 diabetes is diagnosed (1b). At least 50% will need insulin injections if blood glucose is to be maintained at the optimal level regulation (1bF).

There are no controlled comparisons of the effect of the various combinations of drugs on the risk of late complications. Similar information about the new drugs in the area is also lacking.

### 5.1.3 Pharmacological treatment of hypertension

The blood pressure is measured on the upper arm, usually after five minutes of rest. Both the systolic (the upper) and the diastolic (the lower) blood pressure are recorded. Both systolic and diastolic blood pressure are of significance for the risk of cardiovascular disease – the higher, the greater the risk (548) (2b). Depending on age and duration of the diabetes, 40-80% of Type 2 diabetes patients have hypertension (549, 550) (2b).

The WHO has defined the limit for hypertension as a blood pressure permanently greater than or equal to 140/90 mmHg (548). In Type 2 diabetes it is predominantly the systolic blood pressure that is raised.

With hypertension, any overweight should be treated with dietary change, dietary salt reduction and exercise. Apart from that, the treatment is mainly pharmacological with tablets. These classes of drugs have different mechanisms of action, associated effects and possible side effects.

**TABLE 5.1.3.1**

<table>
<thead>
<tr>
<th>Pharmacological classes of antihypertensive drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duretics</td>
</tr>
<tr>
<td>Calcium antagonists</td>
</tr>
<tr>
<td>Beta-blockers</td>
</tr>
<tr>
<td>ACE inhibitors and angiotensin II receptor inhibitors</td>
</tr>
<tr>
<td>Other: Alpha-blockers and centrally active drugs</td>
</tr>
</tbody>
</table>

Many randomised trials of persons with hypertension without diabetes have shown that treatment with antihypertensive drugs reduces the occurrence of stroke and coronary thrombosis (548) (1b). This also applies to the four uppermost classes of drugs in the above table.

With Type 2 diabetes the question, though, is whether anti-hypertensive treatment has the same effect, and if so, whether the treatment goal is the same, and, finally, which antihypertensive drugs should be preferred.

Three different types of randomised trials shed light on these questions (Tables 5.1.3.2 and 5.1.3.3):

- Older studies (551, 552) (1b(F)), in which drugs were compared with placebo
- Studies where the significance of blood pressure achieved through the treatment has been analysed by setting different treatment goals (553, 554) (1b(F))
- Studies where the effect of new drugs was compared with the effect of older drugs after randomisation (554) (1b) (555-557) (1b(F)).

In three of all these studies (UKPDS, ABCD and FACET) all the subjects had Type 2 diabetes, while only few of the subjects in most of the remainder studies had diabetes (approx. 10%). Some of our knowledge thus stems from analyses of such subgroups. The problems with this are discussed in the introduction.

*Does anti-hypertensive treatment affect the risk of cardiovascular disease in Type 2 diabetes?*

The two older placebo-controlled studies SHEP (551) (1b(F)) and Syst-Eur (552) (1b) encompassed 9,000 elderly persons with systolic hypertension (Table 5.1.3.2). Of these, almost 1,100 had known diabetes. The active treatment was either based on a diuretic (SHEP) or a calcium antagonist (Syst-Eur) and in both cases...
compared with inactive placebo. During the course of the studies the blood pressure was lower in the actively
treated groups.

As is apparent from Table 5.1.3.2, these treatments had no effect on the general mortality, but significantly
reduced the risk of serious cardiovascular events in the heart and brain (stroke) and of cardiovascular mortality.

In the HOT Study (553) (1b(F)) 18,790 middle-aged men with diastolic hypertension were randomised to
three different treatment goals for diastolic blood pressure: \( \leq 90 \text{ mmHg} \), \( \leq 85 \text{ mmHg} \) or \( \leq 80 \text{ mmHg} \). The
basic treatment was a calcium antagonist which, depending on attainment of the desired blood pressure, was
supplemented with ACE inhibitor or beta-blocker or finally, with diuretic.

At the beginning of the study, 1,501 of the patients had diabetes (8%).

After 3.8 years there was no difference in the risk of cardiovascular events in the group of persons without
diabetes if those who were treated to a diastolic blood pressure \( \leq 80 \text{ mmHg} \) were compared to those who
were treated to a blood pressure \( \leq 90 \text{ mmHg} \). In contrast, the intensive blood pressure lowering reduced the
mortality and the risk of coronary thrombosis as well as other serious cardiovascular events in the diabetes
group (Table 5.1.3.2). By lowering the diastolic blood pressure from 90 to 80 mmHg for 10 years, one
serious event could be prevented for every eight persons treated.

Treatment of hypertension in Type 2 diabetes thus reduces the risk of cardiovascular disease, and this reduction
seems to be more pronounced compared with the reduction in patients without diabetes.

What blood pressure goal should be aimed at in Type 2 diabetes?
From the HOT Study it appears that the diastolic blood pressure should ideally be treated to below 80 mmHg
in that the risk of a cardiovascular event is thereby halved compared with just treating down to below 90
mmHg (553) (1b(F)).

In parallel with the study of intensive hypoglycaemic treatment in the UKPDS the diabetes patients with
hypertension (1,148) participated in a randomised trial of the effect of anti-hypertensive treatment (554)
(1b). The aim of the study was partly to compare the effect of strict blood pressure control (<150/85 mmHg)
with loose blood pressure control (<180/105 mmHg) and partly to compare ACE inhibitor with beta-blocker
as the basic treatment in the strictly controlled group (558) (1b).

There was no difference in the general mortality in the strictly controlled group compared with the loosely
controlled group (Table 5.1.3.2). However, strict control was accompanied by a reduced risk of “diabetes
related events”, including stroke (0.51 per 100 patient-years) and “microvascular late complications”, mainly
retinopathy (0.72 per 100 patient-years), and diabetes related mortality (Table 5.1.3.2).

By calculating the blood pressure results from the UKPDS as an observation study and comparing the systolic
blood pressure achieved (irrespective of the treatment) with the risk of late complications it was found that
for each 10-mmHg reduction in systolic blood pressure the relative risk of mortality, coronary thrombosis,
stroke, amputations, heart failure and microvascular late complications was reduced by 10-20% (559) (2b).

From this observation study it could also be seen that as with blood glucose, the risk increased exponentially
with increasing systolic blood pressure.

In the HOT study, 50% of the patients had to have two drugs, and 25% had to have three or more drugs
in order to attain a diastolic blood pressure \(<80 \text{ mmHg} \) (553) (1b(F)). In the UKPDS an average blood
pressure of 144/82 was achieved through strict control and 154/87 mmHg through loose control. In the
strict control group, 40% of the patients required two drugs and 30% required three or more drugs (554)
(2b).
TABLE 5.1.3.2
Randomised trials of the value of blood pressure control and the significance of the blood pressure level. Placebo-controlled studies and intensive versus conventional treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary or subgroup analysis</th>
<th>No. of patients at start of project</th>
<th>Duration of follow-up period (yr)</th>
<th>Outcome measure (only the primary outcome measure is stated)</th>
<th>Risk: Events per 100 patient-years</th>
<th>Absolute risk reduction per 100 patient-years</th>
<th>Relative risk reduction</th>
<th>P-value</th>
<th>Number needed to treat, NNT per 10 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHEP</td>
<td>S</td>
<td>583</td>
<td>5</td>
<td>Serious cardiovascular events</td>
<td>4.28</td>
<td>6.30</td>
<td>2.02</td>
<td>&lt;0.05</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>(diuretics vs. placebo)</td>
<td></td>
<td></td>
<td>Serious coronary disease</td>
<td>1.84</td>
<td>3.22</td>
<td>1.38</td>
<td>&lt;0.05</td>
<td>7.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>General mortality</td>
<td>3.50</td>
<td>3.56</td>
<td>0.06</td>
<td>NS</td>
<td>(66.7)</td>
</tr>
<tr>
<td>Syst-Eur (calcium antagonists vs. placebo)</td>
<td>S</td>
<td>492</td>
<td>2</td>
<td>All cardiovascular events</td>
<td>2.20</td>
<td>5.76</td>
<td>3.56</td>
<td>&lt;0.05</td>
<td>7.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cardiovascular mortality</td>
<td>0.83</td>
<td>2.78</td>
<td>1.95</td>
<td>0.01</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>General mortality</td>
<td>2.64</td>
<td>4.51</td>
<td>1.87</td>
<td>0.09</td>
<td>(5.3)</td>
</tr>
<tr>
<td>HOT</td>
<td>S</td>
<td>1501</td>
<td>3.6</td>
<td>Serious cardiovascular events</td>
<td>1.19</td>
<td>2.44</td>
<td>1.25</td>
<td>0.005</td>
<td>8.0</td>
</tr>
<tr>
<td>(intensive vs. conventional treatment)</td>
<td></td>
<td></td>
<td></td>
<td>Acute myocardial infarction</td>
<td>0.37</td>
<td>0.75</td>
<td>0.38</td>
<td>0.01</td>
<td>(26.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cardiovascular mortality</td>
<td>0.37</td>
<td>1.18</td>
<td>0.74</td>
<td>0.016</td>
<td>13.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>General mortality</td>
<td>0.90</td>
<td>1.59</td>
<td>0.69</td>
<td>0.068</td>
<td>(94.9)</td>
</tr>
<tr>
<td>UKPDS</td>
<td>P</td>
<td>1148</td>
<td>8.4</td>
<td>All diabetes related events</td>
<td>5.09</td>
<td>6.74</td>
<td>1.65</td>
<td>0.005</td>
<td>6.1</td>
</tr>
<tr>
<td>(intensive vs. conventional treatment)</td>
<td></td>
<td></td>
<td></td>
<td>Diabetes related mortality</td>
<td>1.37</td>
<td>2.03</td>
<td>0.66</td>
<td>0.019</td>
<td>15.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>General mortality</td>
<td>2.24</td>
<td>2.72</td>
<td>0.48</td>
<td>0.07</td>
<td>(20.8)</td>
</tr>
</tbody>
</table>

Which drugs should be preferred for the treatment of hypertension in Type 2 diabetes?

As mentioned above, a single drug is rarely sufficient if hypertension is to be treated satisfactorily. In the randomised trials that compared different drugs it is thus the basic treatment that is compared. Depending on whether the treatment goal has been achieved, drugs from other classes are given as a supplement. It is moreover characteristic for these studies that they have strived for identical blood pressure levels in the compared groups, and that it is thus the drugs’ properties over and above their anti-hypertensive effect that one investigates.

In the available studies, treatment with ACE inhibitor is compared with other forms of basic treatment (Table 5.1.3.3).

The ABCD study (555) (1b(F)) was not primarily designed to test survival and risk of developing cardiovascular disease with different anti-hypertensive treatments. However, it is the only part of the study that has been published. 470 patients with diastolic hypertension (≤90 mmHg) were treated with either the ACE inhibitor enalapril or the calcium antagonist nisoldipin as the basic treatment for five years, whereafter the study was discontinued. The reason for this was that the frequency of coronary thrombosis was 5-fold higher in the calcium antagonist group. The mortality was not statistically significant, however (Table 5.1.3.3).

In the FACET study (557) (1b(F)) 380 diabetes patients with hypertension were treated for 2.8 years with either the ACE inhibitor fosinopril or the calcium antagonist amlodipin. The study was not designed to investigate survival and cardiovascular disease. Compared with amlodipin, the ACE inhibitor treatment entailed a lower risk of a serious cardiovascular event (coronary thrombosis, serious angina pectoris or stroke).

In the CAPPP study the ACE inhibitor captopril was compared with either beta-blocker or diuretic. The follow-up period was 6.1 years. A total of 10,985 persons were included, of which 572 had diabetes. This study thus comprised a subgroup analysis (560) (1b(F)). With comparable average blood pressures the risk of developing cardiovascular disease was lower with ACE inhibitor as the basic treatment. Moreover, the total mortality was also lower (Table 5.1.3.3).

In the UKPDS Study the ACE inhibitor captopril was compared with the beta-blocker atenolol (558) (1b). Comparable blood pressures were achieved, and no differences in mortality and risk of late complications were found. More patients had to discontinue treatment due to side effects with beta-blocker than with ACE inhibitor. Among other things there was a greater weight increase during the course of the study with beta-blocker (3.4 kg) than with ACE inhibitor (1.6 kg). The frequency of serious hypoglycaemic attacks was the same in the two groups.

The results of these studies have been collated in a meta-analysis (561) (1a), which shows that treatment with ACE inhibitors is accompanied by a lower risk of cardiovascular disease. As the ABCD, FACET and the CAPPP studies are either subject to method-related problems or are subgroup analyses, and as a corresponding
beneficial effect of ACE inhibitors compared with beta-blockers could not be demonstrated in the UKPDS Study, it is not possible to definitely conclude that ACE inhibitors are best as the basic treatment. The same applies to the suspicion that the calcium antagonists should entail a higher risk of unintended effects.

In the LIFE study a subgroup of 1,195 diabetes patients (13% of the total number of patients) with hypertension and cardiac hypertrophy were treated for an average of 4.7 years with either the angiotensin II receptor antagonist losartan or the beta-blocker atenolol as the basic treatment (556) (1b(F)). The treatment with losartan was associated with a lower risk of cardiovascular events and a lower mortality, both generally and as regards cardiovascular disease.

The ALLHAT study encompassed 33,357 patients with light to moderate hypertension and one or more other risk factors, e.g., diabetes (562) (1b). The primary aim of the study was to elucidate the significance of basic treatment with either thiazide diuretic (chlorthalidon), calcium antagonist (amlodipin) or ACE inhibitor (lisinopril) for the risk of fatal or non-fatal heart attacks. Other types of cardiovascular events and heart failure were examined secondarily. After an average of 4.9 years both the general mortality and the risk of heart attacks were compared in all three groups. Diuretic treatment was associated with a lower risk of heart failure compared with each of the other two groups. Among the 12,063 (36%) participating diabetes patients the result was the same. As no concrete figures for the diabetes group are available, no risk reductions can be calculated, and the study is therefore not included in Table 5.1.3.3.

### TABLE 5.1.3.3

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary or Subgroup analysis</th>
<th>No. of patients at start of project</th>
<th>Duration of follow-up period (yr)</th>
<th>Outcome measure (only the primary outcome measure is stated, where these exist) * indicates secondary outcome measure</th>
<th>Risk: Events per 100 patient-years</th>
<th>Absolute risk reduction per 100 patient-years</th>
<th>Relative risk reduction %</th>
<th>P-value</th>
<th>Number needed to treat, NNT per 10 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCD</td>
<td>(enalapril vs. nisoldipin)</td>
<td>P</td>
<td>470</td>
<td>Acute myocardial infarction*</td>
<td>0.43</td>
<td>2.12</td>
<td>1.69</td>
<td>80</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cardiovascular mortality*</td>
<td>0.43</td>
<td>0.85</td>
<td>0.42</td>
<td>50</td>
<td>NS (23.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>General mortality*</td>
<td>1.11</td>
<td>1.45</td>
<td>0.34</td>
<td>23</td>
<td>NS (294)</td>
</tr>
<tr>
<td>FACET</td>
<td>(fosinopril vs. amlodipin)</td>
<td>P</td>
<td>380</td>
<td>All cardiovascular events*</td>
<td>2.6</td>
<td>5.0</td>
<td>2.4</td>
<td>48</td>
<td>0.030</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acute myocardial infarction*</td>
<td>1.8</td>
<td>2.4</td>
<td>0.6</td>
<td>25</td>
<td>NS (66.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>General mortality*</td>
<td>0.7</td>
<td>0.9</td>
<td>0.2</td>
<td>22</td>
<td>NS (50)</td>
</tr>
<tr>
<td>CAPPP</td>
<td>(captopril vs. diuretic/b-blocker)</td>
<td>S</td>
<td>572</td>
<td>All cardiovascular events</td>
<td>1.59</td>
<td>2.68</td>
<td>1.09</td>
<td>41</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acute myocardial infarction*</td>
<td>0.53</td>
<td>1.56</td>
<td>1.03</td>
<td>65</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>General mortality</td>
<td>0.90</td>
<td>1.68</td>
<td>0.78</td>
<td>46</td>
<td>0.034</td>
</tr>
<tr>
<td>UKPDS</td>
<td>(captopril vs. atenolol)</td>
<td>S</td>
<td>1,148</td>
<td>All diabetes related events</td>
<td>5.33</td>
<td>4.84</td>
<td>-0.49</td>
<td>-9</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diabetes related mortality</td>
<td>1.52</td>
<td>1.20</td>
<td>-0.32</td>
<td>-21</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>General mortality</td>
<td>2.36</td>
<td>2.08</td>
<td>-0.30</td>
<td>-13</td>
<td>0.44</td>
</tr>
<tr>
<td>LIFE</td>
<td>(losartan vs. atenolol)</td>
<td>S</td>
<td>1,195</td>
<td>All cardiovascular events</td>
<td>3.92</td>
<td>5.36</td>
<td>1.44</td>
<td>27</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cardiovascular mortality</td>
<td>1.36</td>
<td>2.18</td>
<td>0.82</td>
<td>38</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>General mortality</td>
<td>2.25</td>
<td>3.72</td>
<td>1.47</td>
<td>40</td>
<td>0.003</td>
</tr>
</tbody>
</table>

**Subconclusion**

- There is evidence that pharmacological treatment of hypertension in Type 2 diabetes reduces the risk of cardiovascular disease and mortality. The effect is greater the lower the blood pressure achieved (1b).
- The goal for antihypertensive treatment in Type 2 diabetes stipulated in the guidance report on the diagnosis and treatment of Type 2 diabetes published in the Journal of the Danish Medical Association in 2000 (BP < 135/85) seems to be well founded (1a).
- The most important factor for the prophylactic effect is the fall in blood pressure *per se*, while it is has not yet been finally clarified if, for example ACE inhibitors and/or angiotensin II receptor antagonists offer special advantages compared with the other main classes (1b). Due to the renoprotective effect and the results of the HOPE study (see Sections 5.1.5 and 5.1.6) these drugs should continue to be preferred as the basic treatment until further notice (1b).
- It is unclear whether certain combinations of drugs entail advantages or disadvantages.

### 5.1.4 Pharmacological treatment of the dyslipidaemia

It is common knowledge and confirmed in population studies that raised blood lipid levels increases the risk of cardiovascular disease. When assessing this risk, however, it is important not only to consider how high
the total cholesterol level is, but also to measure and estimate the composition of the lipids in the blood. An increase in the level of certain lipids (LDL cholesterol and triglycerides) and a decrease in others (HDL cholesterol) are both associated with increased risk. In Type 2 diabetes, total cholesterol is not necessarily raised, but its composition is often changed in an unfavourable direction such that triglycerides are too high and HDL cholesterol too low. Moreover, this phenomenon is accompanied by a change in LDL cholesterol that renders it more harmful to the vascular wall. The phenomenon is called dyslipidemia.

Various groups of drug exist that have a beneficial effect on these changes. Those most used and best investigated are statins and fibrates. Statins are often given in order to lower the total and LDL cholesterol levels, while fibrates are often given in order to lower the triglyceride level.

Several major randomised trials have shown that treatment with cholesterol-lowering drugs reduces the risk of both the development of cardiovascular disease and of new heart attacks (293, 294, 563-569) (1b). The question, however, is whether that which applies in general can be transferred to patients with Type 2 diabetes, or whether their situation is different.

With one single exception (293) (1b(F)) there are as yet no published studies of the effect of cholesterol-lowering treatment solely encompassing Type 2 diabetes patients. Thus our knowledge primarily derives from subgroup analyses where subgroups such as Type 2 diabetes patients are first examined after calculation of the results for all subjects. These groups are often inadequately characterised and probably not always representative of Type 2 diabetes patients in general practice and diabetes out-patient clinics.

**Does treatment with lipid-lowering drugs reduce the risk of development of cardiovascular disease in Type 2 diabetes patients without known atherosclerosis in the heart?**

Five RCTs of the prophylactic effect of lipid-lowering treatment have been published that include diabetes patients. A common feature of these studies is that the diabetes groups were small relative to the total number of patients. The Woscops study, the largest and most cited study of primary prevention, only encompassed men without diabetes (563) (1b). The Helsinki Heart Study (565) (1b(F)) tested the effect of fibrate compared with placebo on the combined end points myocardial infarction or cardiovascular mortality. The effect was not statistically significant. In the SENDCAP study (293) (1b(F)) the effect of fibrate on the risk of myocardial thromboses or myocardial ischaemia was assessed by means of electrocardiography (Table 5.1.4.1). A statistically significant risk reduction was found, but in this case myocardial ischaemia was not a factor planned to be investigated from the start.

In the Afcaps/Texcaps study (564) (1b) 155 diabetes patients were treated with statin or placebo without demonstrable effect.

In the Heart Protection Study (HPS) (201) (1b) more than 20,000 patients were randomised to treatment with either statin or placebo. They had either suffered from known heart disease or had a major risk factor such as other forms of atherosclerosis, hypertension, diabetes or a combination of these. Total cholesterol just had to be over 3.5 mmol/l at the start of the study. 5,963 persons with known diabetes participated. Among these, 3,982 did not have known heart disease, but in many cases some other form of atherosclerosis. Even though an increasing number of placebo patients placed on statin treatment during the course of the study (32% after five years for whole patient group), the risk of a serious cardiovascular event (coronary infarct, stroke or vascular surgical intervention) was reduced by 0.96 per 100 patient-years in the statin-treated group compared to the placebo group. There is no information on the effect on general mortality and on cardiovascular disease among the diabetes patients. Neither does the study elucidate the possible effect of statin treatment in diabetes patients without known atherosclerosis.

In the ALLHAT study, 10,355 of the 33,357 patients with hypertension (see above) participated in a randomised trial of the effect of statin versus placebo on mortality and the risk of myocardial infarction (562) (1b). Of these, 35% had diabetes. After in an average of 4.8 years of treatment no statistically significant effect of statin treatment on the mortality and risk of myocardial infarction was detected, neither in the whole group nor in the subgroup of diabetes patients. All these patient were treated for light to moderate hypertension, and 14% had known heart disease. In the latter group LDL cholesterol exceeded 2.6 mmol/l, while in the remainder it exceeded 3.1 mmol/l.
Many Type 2 diabetes patients have atherosclerosis in the heart, and a risk assessment based on possible atherosclerosis in other vessels, dyslipidemia, hypertension, albuminuria and smoking shows that a large proportion of the Type 2 diabetes patients have a high risk of cardiovascular disease and death. As the same risk of myocardial infarction has been found among Finnish Type 2 diabetes patient without known heart disease as among patients without diabetes that have had a myocardial infarct (570) (2b), many are of the opinion – especially after the publication of the Heart Protection Study – that all present risk factors in the diabetes patient, including dyslipidemia, should be treated intensively with drugs. However, a major Scottish observation study, did not find the same great risk among a group of patients with newly detected Type 2 diabetes compared with heart patients without diabetes (571) (2b), and the ALLHAT study indicates that not all diabetes patients can benefit from cholesterol-lowering drugs.

Do lipid-lowering drugs reduce the risk of aggravation of present cardiovascular disease in Type 2 diabetes?

Analyses are available of the participating diabetes groups from five large randomised trials of the prophylactic effect of lipid-lowering drugs. These examined the effect of statin or fibrate treatment on the risk of new serious heart attacks and mortality among patient with known cardiovascular disease (Table 5.1.4.1).

Apart from the LIPID study (568) (1b(F)), these studies all demonstrated a statistically significant risk reduction with both fibrate treatment (VAHIT) (566) (1b(F)) and statin treatment (4S and CARE) (294, 567) (1b(F)). 2-6 patients have to be treated for 10 years to prevent a single new serious cardiovascular event (Table 5.1.4.1).

In the Heart Protection Study (HPS) (201) (1b) 1,981 diabetes patients with known heart disease were treated with either statin or placebo. Statin treatment reduced the risk of serious cardiovascular events by 0.86 per 100 patient-years (NNT 11.6). The possible effect on mortality is not reported. In this study and in a combined assessment of CARE and LIPID (563) (1b(F)) the effect of statin is independent of the measured cholesterol level.

### TABLE 5.1.4.1
Randomised trials of the value of lowering blood lipids

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary or Subgroup analysis</th>
<th>No. of patients at start of project</th>
<th>Duration of follow-up period (yr)</th>
<th>Outcome measure (only the primary outcome measure is stated)</th>
<th>Risk: Events per 100 patient-years</th>
<th>Absolute risk reduction per 100 patient-years</th>
<th>Relative risk reduction</th>
<th>P-value</th>
<th>Number needed to treat, NNT per 10 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFCAPS/TexCAPS Lovastatin vs. placebo Prim. prophyl.</td>
<td>S 155</td>
<td>5.2</td>
<td>Serious cardiovascular events</td>
<td>0.92</td>
<td>1.62</td>
<td>0.70</td>
<td>43</td>
<td>NS (14.3)</td>
<td></td>
</tr>
<tr>
<td>Helsinki Heart Study Gemfibrozil vs. placebo Prim. prophyl.</td>
<td>S 95</td>
<td>5</td>
<td>Myocardial infarction or cardiovascular mortality</td>
<td>0.68</td>
<td>2.31</td>
<td>1.43</td>
<td>68</td>
<td>0.19 (7.0)</td>
<td></td>
</tr>
<tr>
<td>SENDCAP Bezaflorat vs. placebo Prim. prophyl.</td>
<td>P 164</td>
<td>3</td>
<td>Cardiovascular event assessed by ECG</td>
<td>2.06</td>
<td>6.43</td>
<td>4.37</td>
<td>68</td>
<td>0.01 2.3</td>
<td></td>
</tr>
<tr>
<td>HPS Simvastatin vs. placebo Prim. prophyl.</td>
<td>S 3,982</td>
<td>5</td>
<td>Serious cardiovascular events</td>
<td>2.76</td>
<td>3.72</td>
<td>0.96</td>
<td>26</td>
<td>&lt;0.05 10.4</td>
<td></td>
</tr>
<tr>
<td>VAHIT Gemfibrozil vs placebo Sec. prophyl.</td>
<td>U 627</td>
<td>5.1</td>
<td>Myocardial infarction, stroke or cardiovascular mortality</td>
<td>5.58</td>
<td>7.15</td>
<td>1.57</td>
<td>22</td>
<td>0.05 6.4</td>
<td></td>
</tr>
<tr>
<td>4S Simvastatin vs. placebo Sec. prophyl.</td>
<td>S 202</td>
<td>5.4</td>
<td>Serious cardiovascular events</td>
<td>4.23</td>
<td>8.40</td>
<td>4.17</td>
<td>50</td>
<td>0.002 2.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cardiovascular mortality</td>
<td>2.12</td>
<td>3.25</td>
<td>1.13</td>
<td>35</td>
<td>0.242 (8.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>General mortality</td>
<td>2.65</td>
<td>4.58</td>
<td>1.93</td>
<td>42</td>
<td>0.087 (5.2)</td>
<td></td>
</tr>
<tr>
<td>CARE Pravastatin vs. placebo Sec. prophyl.</td>
<td>S 585</td>
<td>5</td>
<td>Myocardial infarction or cardiovascular mortality</td>
<td>5.74</td>
<td>7.37</td>
<td>1.63</td>
<td>22</td>
<td>0.05 6.1</td>
<td></td>
</tr>
<tr>
<td>LIPID Pravastatin vs. placebo Sec. prophyl.</td>
<td>S 782</td>
<td>6.1</td>
<td>Cardiovascular mortality</td>
<td>3.15</td>
<td>3.74</td>
<td>0.59</td>
<td>16</td>
<td>NS (16.9)</td>
<td></td>
</tr>
<tr>
<td>HPS Simvastatin vs. placebo Sec. prophyl.</td>
<td>U 1,981</td>
<td>5</td>
<td>Serious cardiovascular events</td>
<td>6.67</td>
<td>7.55</td>
<td>0.86</td>
<td>11</td>
<td>&lt;0.05 11.6</td>
<td></td>
</tr>
</tbody>
</table>

Subconclusion

- Treatment with the lipid-lowering drugs statins and fibrates reduces the risk of new serious heart attack and death in patients with Type 2 diabetes and known heart disease (1b). The effect is seen at all cholesterol levels.
Randomised trials have not revealed whether these drugs have prophylactic effects on atherosclerosis in all Type 2 diabetes patients. This particularly applies to those for whom the risk is low, while there is evidence that statin treatment reduces the risk of cardiovascular events if the Type 2 diabetes patient has atherosclerosis elsewhere than in the heart (1b).

Observational studies indicate that diabetes patients should receive lipid-lowering treatment in accordance with the same criteria as heart patients if an overall assessment of the risk factors present reveals a high risk (2b).

5.1.5 Treatment of microalbuminuria and albuminuria

As in Type 1 diabetes, Type 2 diabetes also entails the risk of late complications in the kidneys, especially with poor regulation of blood glucose and blood pressure. Diabetic nephropathy is defined as the development of albumin in the urine, which can be demonstrated by means of ordinary urine test strips without any other nephropathy having been demonstrated. Without treatment, approximately half of the patients suffering from diabetic nephropathy will eventually develop impaired renal function and – if they have not died from cardiovascular disease in the meantime – subsequent renal failure.

Nephropathy is preceded by a period of several years in which the patient excretes small, but nevertheless abnormal amounts of albumin in the urine, a condition termed microalbuminuria. Microalbuminuria is a known danger signal for the development of both nephropathy (5-10% per year without treatment) and cardiovascular disease (572, 573) (2b). The possibilities for preventing this development pharmacologically are examined below.

Can microalbuminuria be prevented in Type 2 diabetes?
The relationship between poor blood glucose regulation and the development of microalbuminuria is well substantiated. After nine years of intensive blood glucose regulation in the UKPDS the risk of microalbuminuria tended to be reduced (383) (1b). A corresponding tendency was found after six years of structured follow-up in general practice (574) (1b).

Antihypertensive drugs also have a prophylactic effect, however. Thus treatment of hypertension with both ACE inhibitors, calcium antagonists and beta-blockers reduces the risk of developing microalbuminuria, just as treatment with ACE inhibitors at normal blood pressure also does so (554, 557, 558, 575, 576) (1b).

Is it possible to prevent the progression of microalbuminuria to test strip positive excretion of albumin in the urine and hence to nephropathy?
Intensive blood glucose regulation reduced the risk of developing nephropathy in the little Kumamoto study (540) (1b), and the tendency was the same in the UKPDS study (383) (1b).

With microalbuminuria, antihypertensive treatment will reduce the excretion of albumin and the risk of developing nephropathy.

In contrast to Type 1 diabetes (577), it has not been clearly shown that ACE inhibitors have a renoprotective effect over and above the effect of the blood pressure decrease. Studies of the effect of ACE inhibitors on Type 2 diabetes patients with microalbuminuria without hypertension demonstrate a reduced risk of developing nephropathy, however (572, 575) (1b), but the effect was modest: (MICRO-HOPE) (1b) 0.43 per 100 patient-years, corresponding to an NNT of 23 (Table 5.1.5.1) and possibly attributable to a small difference in blood pressure.

A single randomised trial (IRMA 2) encompassing 590 Type 2 diabetes patients with hypertension and microalbuminuria has shown that just two years of antihypertensive treatment based on the angiotensin II receptor antagonist irbesartan given in moderate or full dosage halves the risk of developing nephropathy (Table 5.1.5.1) (578) (1b). The differences in average blood pressure were very modest as supplementary antihypertensive treatment was given. Please note that NNT in Table 5.1.5.1 is given for three years instead of for 10.

Is it possible to prevent impairment of renal function and renal failure in diabetic nephropathy in Type 2 diabetes patients?
Antihypertensive treatment reduces the decrease in renal function in diabetic nephropathy to approximately half or one third (577).
Two randomised trials encompassing 1,715 (579) (1b) and 1,513 (580) (1b) Type 2 diabetes patients with hypertension and diabetic nephropathy have compared the effect of antihypertensive treatment based on two different angiotensin II receptor antagonists (irbesartan and losartan) with treatment based on the calcium antagonist amlodipin or with placebo tablets (Table 5.1.5.1). Both studies focused on the length of time to a doubling of serum creatinine (expression of renal function) or until renal failure. The studies last 2.6 and 3.4 years, respectively.

Compared with inactive placebo, treatment with angiotensin receptor antagonists resulted in a 2-3% annual reduction in the risk of impaired renal function or renal failure. Compared with the calcium antagonist amlodipin, irbesartan treatment resulted in a 3.3% lower risk of impaired renal function and a 1.6% lower risk of renal failure. The 3-year NNT is shown in Table 5.1.5.1.

### Table 5.1.5.1
Randomised trials of the value of lowering the blood pressure. Angiotensin II receptor antagonists versus other antihypertensive treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary or No. of Subgroup duration of</th>
<th>Outcome measure</th>
<th>Events per 100 patient-years</th>
<th>Absolute risk reduction per 100 patient-years</th>
<th>Relative risk reduction %</th>
<th>P-value</th>
<th>Number needed to treat, NNT per 3 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subgroup analysis</td>
<td>of patients at start of</td>
<td>only the primary outcome</td>
<td>Angiotensin II receptor antagonist</td>
<td>Control treatment</td>
<td>per 100</td>
<td>3 yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>period (yr)</td>
<td>measure (is stated, where this exists)</td>
<td>antagonist</td>
<td>treatment</td>
<td>patient-years</td>
<td></td>
</tr>
<tr>
<td>RENAAAL (losartan vs. placebo)</td>
<td>P</td>
<td>1,531</td>
<td>3.4</td>
<td>Doubling of serum creatinine</td>
<td>7.9</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>End-stage renal failure</td>
<td>6.8</td>
<td>91</td>
<td>2.3</td>
<td>28</td>
<td>0.002</td>
<td>14.5</td>
</tr>
<tr>
<td></td>
<td>General mortality</td>
<td>6.8</td>
<td>6.6</td>
<td>−0.2</td>
<td>−3</td>
<td>0.88</td>
<td>(167)</td>
</tr>
<tr>
<td>IRMA2 (irbesartan 150 mg vs. placebo)</td>
<td>P</td>
<td>396</td>
<td>2</td>
<td>Development of nephropathy</td>
<td>4.87</td>
<td>7.46</td>
<td>2.59</td>
</tr>
<tr>
<td>IDNT (irbesartan vs. placebo)</td>
<td>P</td>
<td>1,148</td>
<td>2.6</td>
<td>Doubling of serum creatinine</td>
<td>6.5</td>
<td>9.4</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>End-stage renal failure</td>
<td>5.4</td>
<td>7.0</td>
<td>1.6</td>
<td>23</td>
<td>0.07</td>
<td>(20.8)</td>
</tr>
<tr>
<td></td>
<td>General mortality</td>
<td>5.8</td>
<td>6.3</td>
<td>0.5</td>
<td>8</td>
<td>0.57</td>
<td>(66.7)</td>
</tr>
<tr>
<td></td>
<td>(irbesartan vs. amlodipin)</td>
<td>P</td>
<td>1,146</td>
<td>2.6</td>
<td>Doubling of serum creatinine</td>
<td>6.5</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>End-stage renal failure</td>
<td>5.4</td>
<td>7.1</td>
<td>1.7</td>
<td>24</td>
<td>0.07</td>
<td>(9.4)</td>
</tr>
<tr>
<td></td>
<td>General mortality</td>
<td>5.8</td>
<td>5.8</td>
<td>−0.0</td>
<td>10.4</td>
<td>0.8</td>
<td>–</td>
</tr>
</tbody>
</table>

**Subconclusion**
- Pharmacological treatment of raised blood pressure reduces the risk of late diabetic complications in the kidneys (1b).
- Much indicates – but it has not yet been documented – that treatment of Type 2 diabetes patients with ACE inhibitors has a special prophylactic effect in this regard (1b).
- It is well documented that the related angiotensin II receptor antagonists both reduce the risk that microalbuminuria will develop into manifest nephropathy, and that the nephropathy will develop into renal failure (1b).

### 5.1.6 Other pharmacological treatment that prevents the development or progression of cardiovascular disease

Evidence-based treatment given to patients with atherosclerosis in the heart, brain or the legs should also be offered to patients with diabetes. Analyses of diabetes groups in large randomised trials of various pharmacological treatments for myocardial infarction have shown that the prophylactic effect in diabetes patients is the same – and in certain cases even greater. Of these treatments, prophylactic treatment with ACE inhibitors and acetylsalicylic acid (ASA) are examined here.

Does ACE inhibitor treatment prevent cardiovascular disease in Type 2 diabetes?

**The Heart Outcomes Prevention Evaluation Study (HOPE)**

As previously mentioned, pharmacological treatment of hypertension with ACE inhibitors reduces the risk of cardiovascular disease. Even though there is no final documentation for this based on randomised trials, quite a few scientific studies nevertheless indicate that ACE inhibitors possess properties over and above the antihypertensive effect that have prophylactic effects on cardiovascular disease.

This hypothesis was tested in the *Heart Outcomes Prevention Evaluation (HOPE) study* (581) (1b(F)) in that 9,297 patients were randomised to treatment with the ACE inhibitor ramipril or with inactive placebo. The
patients had known cardiovascular disease or diabetes with at least one other risk factor. After just 4.5 years of treatment the study was stopped as fewer patients in the ACE inhibitor-treated group had either died from cardiovascular disease or had had a stroke or myocardial infarct.

3,577 of the patients had diabetes (575) \((1b(F))\) at the start of the study. The risk reduction detected in this subgroup was 1.0 per 100 patient-years, corresponding to an NNT of 10. The risk reduction for the individual events is shown in Table 5.1.6.1.

From the subgroup analysis (575) \((1b(F))\), however, it appears that the effect of ramipril was only statistically significant among diabetes patients with diagnosed cardiovascular disease. More than half of the patients had hypertension, and the average blood pressure during the course of the study was lower with ACE inhibitor treatment. This an effect of ramipril through the blood pressure decrease cannot be excluded. Moreover, justified criticism has been raised of the conclusions of the HOPE study as the placebo group were overrepresented with patients with cardiovascular disease and risk factors at the start of the study.

### TABLE 5.1.6.1
Randomised trial of the value of ACE inhibitor treatment. Mixed primary and secondary intervention

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary or Subgroup analysis</th>
<th>No. of patients at start of project</th>
<th>Duration of follow-up period (yr)</th>
<th>Outcome measure (only the primary outcome measure is stated)</th>
<th>Risk: Events per 100 patient-years</th>
<th>Absolute risk reduction per 100 patient-years</th>
<th>Relative risk reduction</th>
<th>P-value</th>
<th>Number needed to treat, NNT per 10 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>MICRO-HOPE</td>
<td>5</td>
<td>3,577</td>
<td>4.5</td>
<td>Myocardial infarction</td>
<td>2.27</td>
<td>2.88</td>
<td>0.61</td>
<td>21</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stroke</td>
<td>0.93</td>
<td>1.36</td>
<td>0.43</td>
<td>32</td>
<td>0.0007</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cardiovascular mortality</td>
<td>1.38</td>
<td>2.16</td>
<td>0.78</td>
<td>36</td>
<td>0.0011</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MManifest nephropathy</td>
<td>1.44</td>
<td>1.87</td>
<td>0.43</td>
<td>23</td>
<td>0.027</td>
</tr>
</tbody>
</table>

**Does acetylsalicylic acid (aspirin) treatment prevent cardiovascular disease in Type 2 diabetes?**

At present it is commonly acknowledged that a small dosage of acetylsalicylic acid has a prophylactic effect and should be offered to all persons with atherosclerosis.

A review of 267 randomised trials – a so-called meta-analysis – comprises a solid scientific foundation for recommending this secondary prophylactic treatment (582) \((1a)\), which consists of the daily intake of 75-150 mg of acetylsalicylic acid.

Acetylsalicylic acid as primary prophylactic treatment for persons without cardiovascular disease has no effect on the mortality, but a modest effect on the risk of myocardial infarction (583) \((1b)\).

In Type 2 diabetes, acetylsalicylic acid treatment has the same secondary prophylactic effect as in patients without diabetes, and the risk is reduced by approx. \(\frac{1}{4}\) (584) \((1b(F))\).

A slightly smaller effect was observed in the HOT study mentioned earlier (553) \((1b(F))\), the effect of 75 mg acetylsalicylic acid on the risk of serious cardiovascular events, myocardial infarction and mortality was tested in parallel to the blood pressure study. No separate figures are available for the 1,501 diabetes patients, but the effect is stated to be of the same magnitude as for all the patients with hypertension (Table 5.1.6.2). The HOT study thus in fact entails mixed primary and secondary prevention as quite a few of the patients had known cardiovascular disease.

In the Physicians' Health Study (583) \((1b(F))\) 533 diabetes patients participated. Acetylsalicylic acid reduced the risk of myocardial infarction by 1.2 per 100 patient-years (Table 5.1.6.2). This study did not take into account the type of diabetes and other risk factors and the presence of cardiovascular disease at the start of the study.

In the Early Treatment Diabetic Retinopathy Study (ETDRS) (585) \((1b(F))\) exclusively encompassed diabetes, but both Type 1 and Type 2. The study also has to be regarded as a mixture of primary and secondary prevention in that approximately half of the patients had known cardiovascular disease at the start of the study. Acetylsalicylic acid reduced the risk of myocardial infarction, while there was no effect on mortality (Table 5.1.6.2). Subgroup analyses of the effect of acetylsalicylic acid treatment in Type 1 and Type 2 diabetes, respectively, showed no statistically significant risk reductions in any of the patient groups.
### TABLE 5.1.6.2
Randomised trials of the value of acetylsalicylic acid treatment. Acetylsalicylic versus placebo

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary or Subgroup analysis</th>
<th>No. of patients at start of project</th>
<th>Duration of follow-up period (yr)</th>
<th>Outcome measure (only the primary outcome measure is stated, where this exists) *indicates secondary outcome measure</th>
<th>Risk: Events per 100 patient-years</th>
<th>Absolute risk reduction per 100 patient-years</th>
<th>Relative risk reduction %</th>
<th>P-value</th>
<th>Number needed to treat, NNT (per 10 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOT (aspirin vs. placebo) diabetes patients and persons without diabetes</td>
<td>S 1,531</td>
<td>3.8</td>
<td>Serious cardiovascular events</td>
<td>0.89</td>
<td>1.05</td>
<td>0.16</td>
<td>15</td>
<td>0.03</td>
<td>62.5</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>0.23</td>
<td>0.36</td>
<td>0.13</td>
<td>36</td>
<td>0.002</td>
<td>77</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>0.37</td>
<td>0.39</td>
<td>0.02</td>
<td>5</td>
<td>0.65</td>
<td>(500)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General mortality</td>
<td>0.8</td>
<td>0.86</td>
<td>0.06</td>
<td>7</td>
<td>0.16</td>
<td>(67)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US Physicians’ Health Study (aspirin vs. placebo) diabetes patients</td>
<td>S 533</td>
<td>5.2</td>
<td>Myocardial infarction</td>
<td>0.77</td>
<td>1.95</td>
<td>1.18</td>
<td>61</td>
<td>&lt;0.01</td>
<td>8.5</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>1.82</td>
<td>2.46</td>
<td>0.64</td>
<td>17</td>
<td>&lt;0.05</td>
<td>15.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General mortality</td>
<td>1.86</td>
<td>2.34</td>
<td>0.38</td>
<td>17</td>
<td>NS</td>
<td>(26.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETDRS (aspirin vs. placebo) diabetes patients</td>
<td>P 3,711</td>
<td>7</td>
<td>Myocardial infarction</td>
<td>2.42</td>
<td>2.98</td>
<td>0.56</td>
<td>19</td>
<td>NS</td>
<td>(17.9)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>2.42</td>
<td>2.98</td>
<td>0.56</td>
<td>19</td>
<td>NS</td>
<td>(17.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Subconclusion**

- Despite the criticism of the HOPE study the result is nevertheless so clear that diabetes patients with cardiovascular disease should be recommended treatment with ACE inhibitors, while there is no evidence suggesting that ACE inhibitors should be given as primary prophylaxis of cardiovascular disease (1b(F)).
- In Type 2 diabetes with manifest cardiovascular disease, prophylactic treatment with acetylsalicylic acid is recommended. However, it is not yet clear what or how many other risk factors have to be present without demonstrable atherosclerosis before acetylsalicylic acid has a prophylactic effect (1a).

#### 5.1.7 Polypharmacological treatment of Type 2 diabetes

With a few exceptions (UKPDS, ALLHAT, ASCOT), the randomised trials discussed in the preceding sections have focused on the effect of treatment of a single risk factor: blood glucose, blood pressure, dyslipidemia or the tendency to form thromboses. The remaining factors have been treated according to “standard practice”, and our knowledge on the significance of various combinations of drugs is thus limited.

Good regulation of the blood glucose level minimises the risk of microvascular late complications, while the effect on the risk of atherosclerosis is not statistically significant.

Most of the patients with known cardiovascular disease included in the randomised trials have been heart patients and only to a minor extent patients with symptoms of atherosclerosis in the heart and the legs. In these cases the evidence for a prophylactic effect of treatment of the risk factors is less well substantiated.

Due to the close relationship to the degree of atherosclerosis in the heart and to the risk factors as well as the very high risk of serious cardiovascular events demonstrated in many observation studies of these patients the Working Group – in accordance with the prevailing European recommendations in the area – recommends that diabetes patients with symptoms of atherosclerosis should be treated according to the same principles at those applying for heart patients.

Which types of serious cardiovascular events have been shown to be preventable in these studies? Primarily coronary infarction and stroke, while there was no measurable effect on amputations.

If the diabetes patient has atherosclerosis in the vessels of the heart, the brain and the legs, the Working Group believes that there is a scientific basis for treating all the demonstrated risk factors. If the blood lipids exceed the recommended limits despite diet and exercise, treatment with a lipid-lowering drug is recommended, primarily a statin. If present, hypertension should be treated intensively, which often requires several drugs. Daily acetylsalicylic acid should be given, and even though no hypertension is present, ACE inhibitor treatment should be considered. In connection with acute myocardial infarction the diabetes patient should probably be intensively treated with insulin (586) (1b).

For the remainder of the patients without signs of atherosclerosis the Working Group recommends carrying out an individual assessment of the risk of a cardiovascular event based on the risk factors: gender, age, smoking, blood pressure, dyslipidemia and albuminuria. The risk over a 10-year period is usually used, and if it is higher than 20% (extrapolated to age 60 years) despite non-pharmacological treatment the patient should be...
recommended intensive pharmacological treatment, but not necessarily polypharmacological treatment. The risk assessment is based on population studies, among others the “Glostrup study”. The practical risk assessment can be undertaken using the common, European risk charts (revised in September 2003), HjerteRask®, Precard/Diacard® or UKPDS Risk Engine version 1.0 (http://www.dtu.ox.ac.uk), which is based on the UKPDS study. The estimated risk-reducing effect of a given treatment, e.g. a fall in blood pressure or cessation of smoking, is not therefore based on randomised trials and is consequently subject to uncertainty. One should nevertheless rely on one of these systems for regular risk assessment of the patients.

In Denmark an intensive polypharmacological treatment strategy has been tested under controlled conditions both in a diabetes outpatient clinic and in general practice.

In the Steno 2 study (333) (1b), 160 patients with Type 2 diabetes and microalbuminuria participated, i.e. patients at high risk of developing late complication in both the small and in the large vessels. Eighty patients were randomised to intensive treatment in a highly specialised diabetes outpatient clinic. The treatment consisted of stepwise implementation of behavioural modification (low-fat diet, increased physical activity and smoking cessation) and polypharmacological treatment of blood glucose, blood pressure and blood lipids. The goal was normalization of all these risk factors. Due to the microalbuminuria all the patients were given ACE inhibitors or angiotensin II receptor antagonists irrespective of the blood pressure, and patients with atherosclerosis were given acetylsalicylic acid (all the patients during the two final years). The remaining 80 patients were assigned to the standard treatment, which was given by the patients’ general practitioner in accordance with current guidelines for diabetes treatment in general practice. The average follow-up period was 7.8 years, during which time intensive treatment resulted in better glucose regulation, lower blood pressure, lower blood lipids and a lower albumin excretion in the urine.

Compared with the standard treatment the intensive treatment reduced the risk of developing of the following late complications:

- Nephropathy, reduced by 2.4 per 100 patient-years (10-yr NNT 4.1)
- Retinopathy, reduced by 2.1 per 100 patient-years (NNT 4.8)
- Late complication in the peripheral nerve, reduced by 3.0 per 100 patient-years (NNT 3.3)
- Cardiovascular mortality, myocardial infarction, coronary interventions or amputation, reduced by 2.6 per 100 patient-years (NNT 3.8) corresponding to a halving.

“Diabetesomsorg i almen praksis” (Diabetes care in general practice) (674) (1b) is a nationwide study encompassing 1,263 patients with newly detected Type 2 diabetes diagnosed at 474 general practitioners. The physicians were randomised to two groups. In the active group the aim was regular follow-up of the patients and the establishment of personal treatment goals for blood glucose, blood pressure, blood lipids and weight. This was supported by written reminders, clinical guidelines and status reports for each patient and courses for the physicians. In the control group the physicians could freely choose and change the treatment. After six years of treatment, blood glucose, blood pressure and cholesterol were lower in the active group and at a level shown in other studies to be associated with a reduced risk of late complications.

Possible advantages and disadvantages of polypharmacological treatment

The scientific literature is virtually devoid of reports on interactions between the drugs mentioned in the preceding chapter. In combination treatment with acetylsalicylic acid and ACE inhibitors a reduction in the total prophylactic effect is suspected. In a recent analysis of data from six large studies of the effect of ACE inhibitor treatment of heart patients (with and without diabetes) the effect on the risk of myocardial infarction was smaller if acetylsalicylic acid was administered concomitantly (587) (1a).

It is well documented, however, that several of the above-mentioned drugs have an effect over and above the intended effect. For example, a reduction of the blood glucose level will have a beneficial effect on the lipids in the blood such that if present, dyslipidaemia will become less pronounced (588) (4). Moreover, a few studies report an antihypertensive effect of the lipid-lowering statins (589) (2b). In another study, statin treatment was associated with a lower incidence of diabetes (590) (2b). Both cases only involve observations, and will have to be tested in randomised trials.

It is well documented that compared with antihypertensive drugs such as ACE inhibitors, the beta-blockers lead to weight gain and a higher blood glucose level (558) (2b), even though their ability to prevent cardiovascular disease is the same. As regards ACE inhibitors and angiotensin II receptor antagonists, moreover, it
has been observed that treatment is accompanied by a reduced risk of development of diabetes (591) (1b) (581) (2b). Once again, though, this will have to be further clarified in randomised trials.

Subconclusion

- All Type 2 diabetes patients should undergo an individual risk assessment as a basis for planning their non-pharmacological and pharmacological treatment (5).
- Type 2 diabetes patients with atherosclerosis elsewhere than in the heart or with accumulated risk factors for cardiovascular disease should be offered regular risk reducing pharmacological treatment (5).
- Polypharmacy has a documented effect in Type 2 diabetes patients with coronary atherosclerosis or with albuminuria should be offered polypharmacological treatment (1b).
- While it is feasible to carry out intensive polypharmacological treatment in highly specialised diabetes outpatient clinics under research conditions, knowledge of how and where the treatment can be most appropriately implemented in routine practice is lacking (1b).
- Structured diabetes care in general practice with the setting of individual treatment goals and systematic follow-up has positive effects on the risk profile in Type 2 diabetes (1b).
- Polypharmacological treatment encompasses several different drugs, and more knowledge is needed about the advantages and disadvantages of various types of treatment combinations (5).

5.2 Organisation

The 1994 National Board of Health report on diabetes treatment in Denmark recommends that general practice should be able to take on the primary responsibility for the treatment of Type 2 diabetes patients whose diabetes is not complicated by other difficult to treat diseases. The diabetes outpatient clinics will have to take care of the treatment of the Type 2 diabetes patients who suffer from severe complications, as well as those patients for whom the treatment goals cannot be achieved in general practice (1) (4).

The above-mentioned recommendation is based on an expert assessment in that there are only few studies of which organizational form ensures most optimal care and treatment of patients with Type 2 diabetes.

What are the components of the organization?

Better care and treatment can be achieved through influencing one or more of the components of the organization, for example:

- The patients and/or the healthcare workers
- Educational possibilities, including motivation and training of the above-mentioned groups
- Unstructured treatment where the individual healthcare workers freely decide what should be offered to the patients, in contrast to structured treatment where the central authorities decide what the patient should be offered and possibly also dictate and defined the forms of cooperation, e.g. shared care with cooperation agreements between the primary and secondary sectors.
- The use of quality assurance systems, for example with computer-generated reminders to patients and healthcare workers in relationship to follow-up visits and examinations.

From science to daily clinical practice – need for health service research

The majority of the medical research addresses technological issues. The scientific results are often obtained under favourable conditions. The studies are often initiated and undertaken by highly motivated personnel whose work mainly concentrates on research. The participants are often selected and motivated patients admitted or referred to admission or to a hospital outpatient clinic. The economic resources and time frames are often better than in the clinical routine. It is therefore far from certain that the same favourable results can be obtained in daily clinical work where the patients are often unselected, where the clinical staff do not have the same education, time and commitment, and where economic and temporal conditions do not necessarily live up to the same standard as in the scientific studies. For example, it has been shown that half of the hypoglycaemic effect disappeared when intensively insulin-treated Type 1 diabetes patients were transferred to a highly specialised diabetes outpatient clinic upon completion of a scientific study (592) (4).

Before research results concerning a new technology is implemented in routine clinical practice it is therefore advisable that the technology is tested within the context of health service research (592) (4). The purpose of health service research is exactly to investigate whether the favourable results obtained under scientific conditions can also be obtained in routine clinical practice. Such studies are cheap to undertake compared to
the costs that will be inflicted upon the health service by just releasing a new technology, for example a new drug (593) (1a). At the same time, they tell the clinicians, patients, administrators and politicians how for example a new drug is most appropriately used, knowledge that rarely exists when new drugs are marketed (593) (1a). As is apparent below, health service research is in short supply, largely due to a lack of prioritisation in connection with the allocation of funding.

Cochrane literature review

The Cochrane Library has published two literature reviews concerning the significance of organizational conditions for the care and treatment of patients with diabetes (512, 594) (1a). These analyses are briefly examined below. The reader is also referred to Annex 7, where the present organisational conditions in Denmark are described.

The purpose of one of the reviews was to elucidate the effect of diabetes treatment in the primary sector and compare the result with follow-up in outpatient clinics/the hospital sector (512) (1a). Five randomised trials encompassing a total of 1,058 patients were identified. The patients were followed for less than two years in four of the five studies. The longest follow-up was five years. Although the study designs differed, a meta-analysis was nevertheless undertaken. A common feature of the studies was that the physicians received education, including clinical guidelines etc. In three of the studies systematic check-up reminders were sent out to both the patients and the physicians.

In the studies in which reminders were sent to the physicians and patients there was no difference in mortality between patients treated in the primary or the secondary sector (OR 1.06, 95% CI 0.53-2.11). HbA1c tended to be lower in the primary sector (OR −0.28, 95% CI −0.59-0.03), while the number of patient who were not followed up was lower in the primary sector (OR 0.37, 95% CI 0.22-0.61). In the studies that did not use well-developed support systems for the general practitioner the results for the patients were poorer. The published studies provide little information about quality of life, risk of cardiovascular disease, functional level and development of complications are only sparsely elucidated. The authors of the literature review concluded: “unstructured care in the community is associated with poorer follow up, greater mortality and worse glycaemic control than hospital care”. Thus these studies support the use of computer-based reminders and review of patient results. The conclusion applies to general practitioners who are willing to participate in studies that offer a structured follow-up. The economic costs for the patients for care and treatment in general practice are lower, while the results of an overall cost-effectiveness analysis are unclear. The authors point out that the studies on which the conclusions are founded are too small to identify differences in the many outcome measure investigated, and that there is a need for an analysis of the economic costs, the patients’ functional status, development of complications, quality of life and duration of hospital admissions. The authors call for health service research to determine which models for cooperation between the health sectors result in the best possible treatment.

The purpose of the other literature review from the Cochrane Library (594) (1a) was to evaluate the effect of various interventions focusing on treatment in the primary and the secondary sectors or on structural and organisational changes. This literature review encompassed 41 studies involving more than 200 practices and 48,000 patients with Type 1 or Type 2 diabetes. Of these, 27 were randomised trials, while 14 were non-randomised. The patients were followed for less than two years in 30 of the studies. The longest follow-up was three years. The studies were so dissimilar as regards the type of intervention, participant composition, size, number of participating practices and outpatient clinics and outcome measure that it was not possible to undertake a meta-analysis. The healthcare personnel received some form of education (written or oral) in nearly all of the 41 studies, and a combination of interventions was used in 38 of the studies. In 12 studies the intervention was exclusively directed towards the healthcare personnel, in 9 towards the organisation and in 20 towards both of these. In 15 studies the intervention was supplemented with patient education. A combined intervention aimed at the healthcare personnel and the organization enhanced the percentage of patients who underwent measurement of blood pressure, blood glucose, HbA1c, weight, cholesterol, serum creatinine and urine analysis, as well as the percentage of patients with follow-up visits and referral to investigation of feet, sight and retina. In contrast, no significant effect on patient goals such as the degree of metabolic regulation or the frequency of complications, hospital admissions and mortality. The authors of the Cochrane review concluded that they could not determine which interventions aimed at the healthcare personnel or which organizational changes were most effective at optimising diabetes treatment. It appears, though, that interventions with a positive effect on clinical practice share the common feature that they include the education of healthcare personnel combined with one or more of the following interventions: Audit, feedback, local consensus meetings, reminders and supervision. Furthermore, the Cochrane review indicates that systematic recall
of the patients for control at the physician can have a beneficial effect on clinical practice. Finally, the Cochrane review indicates that there can also be a positive effect on the patient outcome if a combination of the above interventions are combined with patient education, and/or a nurse is included in the treatment. Nurses can play an important role in the patient-oriented intervention, e.g., in connection with patient education, or as facilitators so that the patients to a higher degree follow the advice given and treatments (compliance). The authors pose virtually the same critical reservations as in the above-mentioned Cochrane analysis and also call for further research in the area.

**Barriers to intensive use of drugs**

Only little is known about organizational barriers to intensive use of drugs. Qualitative interviews indicate that the physicians’ attitude to insulin injections etc. hinders the implementation of this treatment. This treatment is otherwise known to be associated with such great satisfaction among patients with poor glucose regulation that when they have first tried insulin treatment they predominantly choose to continue with it (595) (3). Other studies have shown that the barriers to implementation of diabetes-related evidence are related to the physicians’ age and knowledge (596) (2c), roles and functions (597) (4) and opinion that diabetes is not a serious disease (597) (2c) (595, 598) (3). A single study refutes the notion that physicians do not regard diabetes as a serious disease, however (599) (4).

**Danish experience**

The quality of the diabetes care in both the primary and the secondary sectors far from lives up to the ideal standard recommended in national and international clinical guidelines (600:601) (4). Many diabetes patients do not have their HbA1c measured. Among those who have HbA1c measures it is usually too high. The proportion of patients who undergo eye examinations, and who are referred to podiatrist, seems to be too low (521) (2b). Many Type 2 diabetes patients are treated with two or more drugs due to the concomitant presence of several risk factors, but this is far from being systematic polypharmacy (see the section on economy).

The only study that tests an intensive effort in the form of lifestyle changes and intensive pharmacological treatment of Type 2 diabetes patients is Danish and shows that a strengthened diabetes team within a hospital setting can perform intensive polypharmacy among patients at high risk of cardiovascular and renal disease with the result that fewer complications develop. The effect of lifestyle intervention in this study was marginal (602) (1b).

Another Danish study has shown that the risk factors for Type 2 diabetes patients treated in general practice can be reduced to a level that in other studies has been shown to be able to reduce the development of diabetic complications (574) (1b). Surprisingly the patients did not gain weight, which is otherwise often seen in other studies as a consequence of intensified treatment.

The two Danish studies supplement each other in that the study in general practice supports the value of education of general practitioners supplemented with systematisation of follow-up and polypharmacological treatment guided by individual treatment goals, while the hospital-based study supports the value of a well-developed treatment team in outpatient clinics that can take care of patients with serious complications.

If the methods from these studies have to be implemented in routine clinical practice, resources will have to be allocated, partly with a view to education of physicians and other healthcare professionals, partly with a view to systematising the follow-up. As is apparent from the economy section, however, education is very cheap compared to the other expenses for polypharmacy.

A third Danish-initiated study, Addition, has just started. This study examines the effect of case finding of persons with undetected diabetes in general practice in Denmark, England and Holland. Moreover, the Addition study assesses the effect of educating general practitioners in motivating dialogue and the use of intensive polypharmacy. The results regarding screening are expected to be published within two years, while the effect of the treatment is expected to be published after the 5-year follow-up (37) (5).

**Perspectives**

There is a considerable need for non industry-dependent education of general practitioners in more intensive and knowledge-based use of drugs. Such education is presently provided by the medical industry, which is inappropriate as it has clear economic interests in a greater consumption of drugs. It is estimated that two 4-hr sessions of industry-independent education of general practitioners at 4-year intervals would improve the...
use of drugs among Type 2 diabetes patients in general practice. Knowledge alone is not sufficient to improve quality, however. An effective approach seems to be to combine a combination of interventions directed at the health personnel with education of the patients, and/or if a nurse is included in the treatment. There has to be time to inform, motivate and activate the patients. In this context it is worrying that the number of general practitioners is decreasing, while more tasks are concomitantly being assigned to general practitioners as this could entail a lower threshold for referring patients to diabetes outpatient clinics with a consequent increase in demand for resources. Whether an increased use of nurses in general practice can redress this situation is unclear.

Systematic recall-up of patients for control in general practice can have a beneficial effect on clinical practice. Thus it could be relevant to investigate the effect of introducing a system that many dentists use for summoning patients for dental check-ups. Moreover, it could be interesting to investigate the effect of a professional service in general practice in the form of annual diabetes control on similar lines to the prophylactic consultations for ischaemic heart disease. No studies are available that demonstrate the effect of an economic incentive, however.

There is a considerable lack of health service research evaluating which organizational initiatives could improve the quality of diabetes care in Denmark, including which initiatives should be prioritised. It cannot be excluded that organizational initiatives aimed at improving the general quality of the diabetes care are a better investment than such approaches as intensive use of drugs or screening for undetected diabetes. A debate is needed on the obligations and possibilities of the healthcare personnel regarding further education and participation in quality enhancement and health service research.

**SubConclusion**
- Only sparse documentation is available regarding which organizational form in Denmark could best ensure that all Type 2 diabetes patients receive good and uniform offers of pharmacological treatment (4).
- Diabetes care can be improved through the use of computers and databases to register the quality of the diabetes care and to send out reminders to patients and physicians and through structured cooperation between the primary and the secondary sectors – such as recommended in the National Board of Health’s 1994 memorandum (1a).
- A combination of interventions directed at the healthcare personnel, including the inclusion of nurses in diabetes treatment in general practice and patient education and the establishment of individual treatment goals can improve the general quality of treatment (1a).
- No documentation is available, however, indicating which professional groups are best suited to carry out the information, education, motivation and follow-up tasks associated with more intensive use of drugs (1a).
- Little is known about what barriers exist within the organization and among healthcare workers and patients to more intensive use of drugs (2c). This use of drugs requires structured further education of general practitioners and their staff as well as the allocation of resources (see economy section) (5).
- There is a great need for health service research able to elucidate which organizational initiatives, including the use of polypharmacy, will improve diabetes care (4).

5.3 The patient aspect

This review of the patient aspect solely focuses on how polypharmacological treatment influences on contact to the health service, risk factor level and quality of life among Type 2 diabetes patients. In addition, the possible barriers to patient acceptance of polypharmacological treatment will be briefly reviewed. The patient aspect of lifestyle change is addressed in Chapter 4.

5.3.1 Reasons for contacting the health service

By establishing polypharmacological treatment it must be expected that the number of planned contacts will increase. For example, frequent control of the patient and his well-being will be necessary at the start of polypharmacological treatment in order to find the best combination of drugs and to avoid side effects and interactions. On the other hand, no increase is expected in either the number of spontaneous contacts to the health service due the patient’s diabetes treatment or the number of contacts to the health service for other reasons.
5.3.2 Significance of pharmacological and polypharmacological treatment for the patient

The following is based on patients’ attitudes and experiences with medical treatment in general as no reviews exist of the views of diabetes patients concerning polypharmacological treatment. As there are very few studies with a high evidence level, sources with lower evidence rating have also been used in this chapter. No studies exist that describe the experiences of diabetes patients concerning intensification of the pharmacological treatment of several risk factors. Most patients perceive of the transition from tablet treatment to insulin treatment as a significant change in their everyday lives. In the following the focus will be on patients’ perception of well-being (Quality of Life) with intensified hyperglycaemic treatment.

Most of the polypharmacological treatment is given in order to reduce the risk of developing diabetic complications, not in order to remove symptoms. It is exactly the presence of diabetic complications that is purported to explain why Type 2 diabetes patients assess their quality of life as being worse than for persons without diabetes (603, 604) (2b) (605). Moreover, some diabetes patients will be so badly regulated that intensified treatment will also alleviate the symptoms of the disease and hence also enhance their quality of life (606) (2b).

One randomised trial indicates that better glycaemic regulation is sometimes perceived of as a burden in daily life despite measurable improvement in glycaemic regulation (607) (1b). In another study, however, the patients were more satisfied with the intensive treatment (insulin) even though they felt more ill than a control group that did not need insulin in order to achieve the same good regulation (606) (2b). Furthermore, older Type 2 diabetes patients in insulin treatment report that their quality of life is poorer than among patients on tablet and/or dietary treatment, even though other factors are controlled (608) (2b). This has not been found in Type 2 diabetes patients treated in general practice, however, where no difference in the patients’ assessment of their quality of life is found whether they are treated with or without insulin (609) (2b). However, patients on insulin treatment report more problems as regards pains and social contact (609) (2b).

A possible explanation for these conflicting results on insulin treatment and the assessment of quality of life is that insulin treatment and quality of life should be viewed in relation to whether the patients had poor blood glucose regulation with symptoms prior to initiation of insulin treatment, and whether both the blood glucose regulation and the severity of symptoms have improved (610) (2b). With poor diabetic regulation, insulin treatment thus does not reduce the quality of life (611) (1b) (612) (1b). 89-100% of patients who started insulin treatment as part of a scientific study chose to continue with this after completion of the study (605, 613, 614) (4).

Notwithstanding that the patients’ daily life is affected by having to take medicine, it transpires that it is less interfering to take medicine than to have to change lifestyle and dietary habits (615, 616) (2b).

5.3.3 Barriers to polypharmacological treatment

There are several barriers to polypharmacological treatment, albeit that little is known about this in diabetes. The barriers focused on in the following section are therefore related to treatment-related side-effects, dosage-related problems and factors of significance for whether the physician initiates optimal treatment of the diabetes – also including the patient’s and the physician’s attitude to insulin treatment.

The typical barriers to medical treatment seen from the patient side are the following:

- The lack of appreciable effect of the treatment, either because the patient does not have symptoms that justify treatment, or because the patient does not feel alleviation of the symptoms following initiation of the treatment (607) (1b) (610) (2b).
- The treatment has side-effects (617) (4).
- Dosage is difficult to handle, for example due to the number of doses per day (618) (1a) (619) (1b) (620) (2b), the time for the administration, packaging, and/or problems with taking the medicine.
- The patient’s perception of his disease (617) (4) differs from the medical perception.
- Failure to accept having a chronic disease (446) (2b) (598) (2c) and hence also failure to comprehend that treatment is necessary to prevent complications in the future.
- A reasoned “No, thank you” based on the perception that the costs (e.g. in the form of apprehension for interference with the freedom of the daily life as well as possible side-effects from taking the medicine) are not outweighed by the personal advantages of the treatment such as postponement of complications and/or fewer symptoms.
Economic, social and/or work-related factors (617) (4).
- Inadequate social support (621) (2b).
- Inadequate knowledge (446) (2b) (598) (2c).

In the patients in whom polypharmacological treatment results in improved blood glucose regulation there is a risk that the number of hypoglycaemic attacks will increase (622) (2a), which among other things was the experience of the UKPDS study (383) (1b).

In addition, most of the studies show that an optimisation of blood glucose regulation is accompanied by weight gain (623) (1b). In contrast, a more recent Danish randomised trial undertaken in general practice has demonstrated blood glucose levels corresponding to those in the English study (UKPDS), but without weight gain (574) (1b).

All marketed drugs have been tested for side effects prior to being placed on the market. This has been done by administering the drugs alone, however, and it is not possible to carry out large randomised trials to determine the occurrence of side effects when several types of drug are administered simultaneously. This makes it impossible to say anything about the type and frequency of side effects for the individual drug when it is to be given in combination with other drugs. It is therefore also difficult to explain the risk of side effects in the individual patient before the start of a new treatment (624) (4). On one hand it is not very likely that there will be frequent unknown side effects of the polypharmacological treatments that it is intended to introduce as many diabetes patients have already been receiving this kind of treatment for many years. On the other hand it is known that side effects of polypharmacological treatment can sometimes arise many years after a new drug has been marketed. These side effects are usually rare and serious, as was the case with for example a new antidiabetic drug (625) (1a) and a new cholesterol-lowering drug (626) (4).

5.3.4 Drug dosage in connection with polypharmacy
Dosage can also comprise a barrier to polypharmacological treatment. It can be expected that dosage-related problems would be counteracted by the absence of symptoms, but it has surprisingly transpired that there is no clear correlation between alleviation of symptoms and patient compliance (627) (2b). A possible explanation is that in some cases it is less problematic for the patient to deal with symptoms in daily life than to follow a treatment regime (628) (1b). The greatest barrier to optimal compliance seems to be the number of times per day that the medicine has to be taken (618) (1a) (619) (1b). If the medicine is distributed over more than two occasions per day, compliance is poorer (628) (1b) (629) (4). This has also been found in studies encompassing patients with Type 2 diabetes in oral antidiabetic treatment (620) (2b). Whether this also applies to hypoglycaemic agents administered at mealtimes (tablets or insulin) is not apparent from the available literature.

5.3.5 The patient’s attitude to polypharmacy
Follow-up studies show that between 5 and 10% of diabetes patients do not have any contact with the health service (616) (2b). This is especially so with patients with newly diagnosed diabetes. The number of diabetes patients who say “No, thank you” to polypharmacological treatment if this is indicated on the basis of an assessment of the patient’s risk profile, is not known. In contrast, we do know that many diabetes patients in Denmark are already on polypharmacological treatment at the present time. In Aarhus County just under 80% of all Type 2 diabetes patients receive pharmacological treatment with either hypoglycaemic, antihypertensive or cholesterol-lowering drugs. The number of patients who will accept full polypharmacological treatment in everyday life if it is indicated, is unknown. Based on the literature concerning compliance in chronic diseases it is estimated that 50-70% of the prescribed medicine is taken (630) (1b) (631) (2b) (615) (2b). Apart from patient barriers to polypharmacological treatment there can also be barriers from the side of the treating physician, as mentioned in the section on organization.

5.3.6 Successful implementation of polypharmacological treatment
In the above review we have presented barriers to polypharmacological treatment. These will have to be considered before polypharmacological treatment can be successfully implemented. Primarily the patient will have to be maximally involved in the decision to intensify the treatment and subsequently in the treatment itself. Only well-informed patients who understand their disease will be motivated for long-term intensive polypharmacological treatment if this is medically required (632) (4). In order to motivate the patient to continue to take the medication it is important to take into account both the number of tablets and the distribution of these throughout the day. Finally it is recommended that the patient is followed closely both...
in the start-up phase with new medicine and at time where there are changes in the disease state so as to
prevent side-effects and interactions from the medicine.

Subconclusion
■ There is a distinct need for studies showing what information patients desire and need in order to be
able to participate in the decision to initiate pharmacological treatment and in the regular adjustment of
it (5).
■ Studies are also needed of how to motivate patients to undergo permanent, often lifelong pharmacological
treatment. Patients want full information concerning all treatment possibilities at the time the diagnosis
is made, as well as information about how the disease and treatment will progress (4).
■ Side effects associated with the use of a single drug are well known, whereas little is known about the
frequency and type of side effects associated with the use of several drugs concomitantly (polypharmacy)
(4).
■ Little is known about patient attitudes, quality of life and experience of treatment when prescribed many
different drugs concomitantly (polypharmacy) (5).

5.4 Economy

This section concerns the socio-economic consequences of pharmacological treatment of Type 2 diabetes and
attempts to answer the following questions:
■ What are the total direct costs for regular control and pharmacological treatment of Type 2 diabetes?
■ To what extent is polypharmacological treatment in use at present?
■ What is the relationship between costs and effects with intensive polypharmacological treatment?
■ Do alternative ways of organising the treatment affect the total costs and the relationship between costs
and effects?

The present costs for control and treatment of Type 2 diabetes patients are described using Danish data.
Expected costs for a possible intensified treatment with drugs are calculated based on expert assessment of
the extra consumption of personnel, drugs etc.

No Danish cost-effectiveness analyses have been made of intensified pharmacological treatment of Type 2
diabetes, and it is beyond the temporal and economic scope of this HTA report to carry out such analyses.
Results of foreign economic analyses cannot be immediately transferred to Danish conditions due to differ-
ences in treatment practice and costs. However, foreign analyses can provide an indication of the relationship
between costs and effects. The existing foreign analyses of intensified treatment of diabetes with several types
of drug are therefore reviewed here.

5.4.1 The present extent of polypharmacological treatment

Using figures from the register of Type 2 diabetes patients in Aarhus County it is possible to determine the
degree of polypharmacy with the current treatment practice. The register data are used intensively in the
following. The method used to establish the register is described in Annex 8.

The majority of Type 2 diabetes patients are treated pharmacologically, 13% are treated non-pharmacologi-
cally, while only 8% of the patients are currently treated concomitantly with hypoglycaemic, anti-hypertensive
and lipid-lowering drugs (Figure 5.4.1)

20%, 35% and 1% of the Type 2 diabetes patients, respectively, receive two or more drugs concomitantly
for the treatment of hyperglycaemia, hypertension and dyslipidemia (Figure 5.4.2).
FIGURE 5.4.1 Treatment of Type 2 diabetes in Aarhus County apportioned by treatment approach (non-pharmacological, pharmacological and polypharmacological)

TREATMENT OF TYPE 2 DIABETES IN AARHUS COUNTY

- Non-pharmacological treatment: 8%
- Pharmacological treatment: 13%
- Intensive polypharmacological treatment: 79%

Source: Data from the project: "Monitoring of Type 2 diabetes in Aarhus County" by Jette Kolding Kristensen, MD, PhD (520).

Note: Intensive polypharmacological treatment is defined as concomitant treatment of hypoglycaemic agents, antihypertensive drugs and lipid-lowering agents.

FIGURE 5.4.2 Treatment of Type 2 diabetes in Aarhus County. Antidiabetic, antihypertensive and lipid-lowering treatment

TREATMENT OF TYPE 2 DIABETES IN AARHUS COUNTY

- Lipid-lowering treatment
- Antihypertensive treatment
- Antidiabetic treatment

Proportion under drug treatment

1 drug
2 or more drugs

Source: Data from the project: "Monitoring of Type 2 diabetes in Aarhus County" by Jette Kolding Kristensen, MD, PhD (520).

5.4.2 Current treatment practice, resource consumption and costs

By far the majority (85%) of Danish Type 2 diabetes patients are controlled in general practice without the use of the hospital system’s diabetes outpatient clinics (520). Resource consumption and costs per patient per year are described in Table 5.4.1. The resource consumption and the costs are restricted to regular control and pharmaceutical treatment of the risk factors mentioned in this section. Hospital admissions, control/screening for diabetic changes in the eyes and feet and treatment of diabetic/diabetes complications are not included in the calculations. The costs for control and treatment have been calculated as the total direct treatment costs, i.e. the costs are included irrespective of who pays, but that indirect costs for the patients such as time consumption/lost earnings are not included. The unit costs are based on the Health Insurance fees (17), DRG fees (633) and on the fees charged by a private laboratory (18) and are documented in Annex 413. The costs for control and medical treatment amount to approx. DKK 4,900 per patient per year, of which 70% are drug costs.

13 Fees are not necessarily equal to the real costs. The laboratory fees are based on detailed cost calculations, which on a more general level also applies to DRG fees. No cost studies are available in the health insurance area to elucidate possible deviations between the negotiated fees and the real costs. Moreover, health insurance fees and laboratory fees have the advantage that they reflect the real costs that the public authorities have to cover in the event of a change in the level of activity.
TABLE 5.4.1
Current treatment practice, resource consumption and costs in DKK

<table>
<thead>
<tr>
<th>Personnel consumption/Contacts to the healthcare system</th>
<th>No. visits/person/yr</th>
<th>Costs/person/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit to general practitioner (a)</td>
<td>3.6</td>
<td>362</td>
</tr>
<tr>
<td>Diabetes outpatient clinic visit (b)</td>
<td>0.2</td>
<td>33</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>675</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medicine [percentage under treatment]</th>
<th>% under treatment</th>
<th>Costs/person/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose regulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OHA</td>
<td>52%</td>
<td>611</td>
</tr>
<tr>
<td>Insulin</td>
<td>9%</td>
<td>678</td>
</tr>
<tr>
<td>OHA insulin</td>
<td>5%</td>
<td>435</td>
</tr>
<tr>
<td>Lipid-lowering [c]</td>
<td>14%</td>
<td>561</td>
</tr>
<tr>
<td>Antihypertensive [c]</td>
<td>63%</td>
<td>133</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>20%</td>
<td>36</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>3,434</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other resource consumption (biochemistry)</th>
<th>No./yr</th>
<th>Costs/person/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose strips</td>
<td>20</td>
<td>140</td>
</tr>
<tr>
<td>Blood glucose (general practitioner)</td>
<td>2.7</td>
<td>127</td>
</tr>
<tr>
<td>HbA1c</td>
<td>3.3</td>
<td>435</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.2</td>
<td>21</td>
</tr>
<tr>
<td>Urine albumin/-creatinine</td>
<td>0.5</td>
<td>53</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>796</td>
</tr>
</tbody>
</table>

| Control and treatment costs, total                       |                      | 4,906           |

(a) The figure is adjusted for (exclusive) non-diabetes related consultations. Danes over 46 years and older have 3.6 consultations in average.
(b) This includes a dietician etc.
(c) These figures are for all Type 2 diabetes patients.
Source: Data from the project: “Monitoring of Type 2 diabetes in Aarhus County” by Dr. Jette Kolding Kristensen (520) except that the figures for cholesterol, urine albumin and anticoagulation treatment are the qualified estimates of the Working Group.

If assumed that treatment practices are identical in Aarhus County and in the whole of Denmark and that there are approx. 110,000 known Type 2 diabetes patients in Denmark (634), the total costs for regular control and pharmacological treatment of Type 2 diabetes patients in Denmark can be calculated at just over DKK 0.5 billion (excludes screening, treatment of complications and diabetes-related admission costs).

5.4.3 Intensive systematic polypharmacy, resource consumption and costs

Intensified treatment with many drugs with the aim of achieving optimal control of all risk factors will require considerably more resources, presumably both a greater consumption of drugs and a greater consumption of personnel and other services. As such an intensified, polypharmacological treatment form has not been tested in general practice in Denmark, no data exist indicating how the additional resource consumption will be. Due to the lack of concrete data, expert assessments of the expected extra resource consumption have been made. These assessments are presented in Table 5.4.2 for a risk group of Type 2 diabetes patients with microalbuminuria/albuminuria and/or coronary atherosclerosis.

In order to describe the possible economic consequences of increased use of intensive polypharmacological treatment of Type 2 diabetes in Denmark we use in the following two scenarios for organisation of the treatment, here denoted “systemic polypharmacy” and “realistic polypharmacy”.

We define these two scenarios as follows:

- **Systematic polypharmacy** means that all Type 2 diabetes patients with a given indication (e.g. microalbuminuria and/or previous coronary atherosclerosis) are treated with all the drugs and in the dosage recommended based on scientific evidence. This therefore describes the maximal costs of pharmacological treatment of Type 2 diabetes.

- **Realistic polypharmacy** describes a world where it is taken into consideration that not all patients are offered, tolerate, desire or can be bothered to concomitantly take drugs with an effect on blood glucose, blood pressure and cholesterol and with an anti-coagulating effect (acetylsalicylic acid) as well as drugs for any other chronic diseases they might have. Based on the available literature and other knowledge combined with a consensus within the Working Group we have estimated the percentage of the patients that can realistically be expected to undergo polypharmacological treatment once the necessary organisation – including education – has been established.
## TABLE 5.4.2
Expected resource consumption with intensive systematic polypharmacy. Patients with microalbuminuria/albuminuria and/or previous coronary atherosclerosis

<table>
<thead>
<tr>
<th>Personnel consumption/Contacts to the healthcare system</th>
<th>Current treatment (risk population)</th>
<th>Systematic polypharmacy</th>
<th>Realistic polypharmacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit to general practitioner (a)</td>
<td>4.5</td>
<td>4.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Diabetes outpatient clinic visit (b)</td>
<td>0.6</td>
<td>3.0</td>
<td>10</td>
</tr>
<tr>
<td>Medicine (percentage under treatment)</td>
<td>% under treatment</td>
<td>% under treatment</td>
<td>% under treatment</td>
</tr>
<tr>
<td>Blood glucose regulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OHA</td>
<td>70%</td>
<td>50%</td>
<td>65%</td>
</tr>
<tr>
<td>Insulin</td>
<td>18%</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>OHA + insulin</td>
<td>12%</td>
<td>40%</td>
<td>30%</td>
</tr>
<tr>
<td>Lipid-lowering (c)</td>
<td>14%</td>
<td>100%</td>
<td>70%</td>
</tr>
<tr>
<td>Antihypertensive (c)</td>
<td>63%</td>
<td>100%</td>
<td>70%</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>40%</td>
<td>100%</td>
<td>70%</td>
</tr>
<tr>
<td>Other resource consumption (biochemistry)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood glucose strips</td>
<td>50</td>
<td>200</td>
<td>100</td>
</tr>
<tr>
<td>Blood glucose (general practitioner)</td>
<td>2.7</td>
<td>4.0</td>
<td>3.5</td>
</tr>
<tr>
<td>HbA1c</td>
<td>3.3</td>
<td>4.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.5</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Urine albumin/creatinine</td>
<td>0.5</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Notes: Values for expected resource consumption with systematic and realistic polypharmacy are expert assessments. The values were derived by consensus-establishment\(^{14}\) in the Subgroup for Pharmacological Treatment and subsequently accepted as acceptable estimates buy the whole HTA Project Group.

Resource consumption with systematic and realistic polypharmacy is expected to be the same for persons in the risk group with microalbuminuria/albuminuria and/or atherosclerotic disease in the heart as for other Type 2 diabetes patients.

The figures for current treatment practice are based on a group receiving concomitant antidiabetic, antihypertensive and lipid-lowering treatment. These figures may be considered estimates for the values in the risk group with microalbuminuria/albuminuria and/or atherosclerotic disease in the heart.

It is assumed that there are no patients in this special risk group whose blood glucose is solely regulated non pharmacologically.

(a) The figure is exclusively non-diabetes related consultations. Danes aged 46 years and older have 3.6 consultations in average.

(b) This includes a dietician etc.

(c) These figures are for all Type 2 diabetes patients.

Source (current treatment): Data from the project: "Monitoring of Type 2 diabetes in Aarhus County" by Dr. Jette Kolding Kristensen (520) except that the figures for cholesterol, urine albumin and anticoagulation treatment are the qualified estimates of the Working Group. The percentage of patients being treatment with 1, 2 and 3 or more antihypertensive drugs are the qualified estimates of the Working Group based on data from the Aarhus register, the project "Diabetes care in general practice" and the UKPDS and HDF studies.

Even though many general practitioners have a good knowledge of the elements of optimal diabetes treatment it is considered necessary with both systematic and realistic polypharmacy that all general practitioners undergo extraordinary training (2×4 hours)\(^{15}\).

There will therefore be start-up costs for courses and to cover the general practitioners’ lost earnings. These start-up costs are estimated at DKK 7-18 million\(^{16}\) (Table 5.4.3). An important foundation for increased use of polypharmacological treatment in general practice will be revised clinical guidelines. As such guidelines will probably be prepared in any case, the cost has not been included here.

Based on the resource consumption in Table 5.4.2 and relevant unit costs the present total costs per person per year for control and treatment are estimated at approx. DKK 8,600 for persons with microalbuminuria/albuminuria and/or coronary atherosclerosis, while the costs for systematic and realistic polypharmacological treatment are estimated at DKK 20,500 and 13,200 per person per year, respectively\(^{17}\). These costs can be

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14 Consensus-establishment encompasses individual expert assessments. Presentation of mean, maximum and minimum in the group and subsequent discussion aimed at the establishment of a consensus around an estimate.

15 Costs for further education of general practitioners are not included as it is assumed that the content but not the total extent of the education will change if polypharmacological treatment becomes widespread.

16 The participation percentage is estimated at 100% for systematic polypharmacy and 40% for realistic polypharmacy.

17 This assumes an unchanged product mix. In practice, though, enhanced use of polypharmacy could entail a shift towards more expensive drugs.
compared with the current average control and treatment costs of DKK 4,900 per person per year for all Type 2 diabetes patients considered as a group (Table 5.4.1).

The additional costs associated with the introduction of intensive polypharmacological treatment in Denmark are calculated as the number of affected diabetes patients times the difference in the costs per person per year between the present situation and a possible future situation with systematic or realistic polypharmacological treatment.

It is estimated that implementation of intensive pharmacological treatment of all Type 2 diabetes patients in Denmark will entail annual additional costs in the order of magnitude of between DKK 0.9 billion (realistic polypharmacy) and 1.7 billion (systematic polypharmacy), cf. Table 5.4.3. In round figures, this corresponds to a 3-fold or 4-fold increase, respectively, on the current costs.

The cost estimate is based on expert assessments of the additional resource consumption (Table 5.4.2) and the estimated costs per person per year as well as on assumption that treatment practice in Aarhus County does not differ from that of the rest of Denmark.

There will also be start-up costs, but these will be insignificant (DKK 7-18 million) relative to the annual costs.

Patients with microalbuminuria/albuminuria and/or coronary atherosclerosis comprise a special risk group which, based on an overall assessment, is estimated to benefit from intensive polypharmacological treatment. The number of persons in this group is not known, but can on the basis of the Danish project “Diabetesom-sorg i almen praksis” (Diabetes care in general practice) is estimated to correspond to approx. 48% of Type 2 diabetes patients (635) or approx. 53,000 persons.

Intensive polypharmacological treatment of this risk group will entail annual additional cost of between DKK 250 million (realistic polypharmacy) and DKK 630 million (systematic polypharmacy) cf. Table 5.4.3. Thus the total expenses for treatment and control of Type 2 diabetes patients will increase by 46-117%. In this case too there will be start-up costs of DKK 7-18 million.

The estimated costs of systematic and realistic polypharmacy are based on the current population of known Type 2 diabetes patients. If some form of screening for Type 2 diabetes is concomitantly introduced the costs for polypharmacological treatment could increase significantly if the diabetes patients identified through screening are also to be offered intensive polypharmacological treatment.

<table>
<thead>
<tr>
<th>TABLE 5.4.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional costs of intensive polypharmacological treatment of Type 2 diabetes patients in Denmark</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment offered to all Type 2 diabetes patients</th>
<th>Annual costs (DKK)</th>
<th>Start-up costs (DKK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic polypharmacy</td>
<td>1,720,000,000</td>
<td>18,000,000</td>
</tr>
<tr>
<td>Realistic polypharmacy</td>
<td>920,000,000</td>
<td>7,000,000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment offered to Type 2 diabetes patients at particularly great high risk of developing late complications</th>
<th>Annual costs (DKK)</th>
<th>Start-up costs (DKK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic polypharmacy</td>
<td>630,000,000</td>
<td>18,000,000</td>
</tr>
<tr>
<td>Realistic polypharmacy</td>
<td>250,000,000</td>
<td>7,000,000</td>
</tr>
</tbody>
</table>

5.4.4 Intensive systematic polypharmacy, relationship between costs and effects

The literature search did not identify any cost-effectiveness analyses of simultaneous intensive polypharmacological treatment of several risk factors. A Danish study of the cost-effectiveness of intensive polypharmacological treatment of Type 2 diabetes patients identified by screening has been initiated, but the results will not be available for 6-7 years (37).

Three analyses assessed the cost-effectiveness of intensive polypharmacological treatment of one risk factor, and one analysis assessed in three separate analyses the cost-effectiveness of polypharmacological intervention directed at two risk factors and monopharmacological intervention directed at a third risk factor (Table 5.4.4).
Intensive polypharmacological glycaemic control

In an American analysis a simulation model was employed that uses existing knowledge from epidemiological and controlled clinical trials to estimate the consequences of intensive polypharmacological glycaemic control on life expectancy, quality of life and the costs in the patient's remaining lifetime (72). The costs per gained quality-adjusted life-year were approx. USD 16,000 (DKK 130,000) for the baseline scenario. Intensive glycaemic control was more cost-effective for younger persons than for older persons. Apart from the fact that the study was based on American costs and clinical practice, there are also a number of other limitations to the model. The results should therefore be interpreted with caution (Table 5.4.4). In another corresponding model study the costs per quality-adjusted life-year were approx. USD 41,000 (DKK 330,000) for the baseline scenario based on expected resource consumption in the USA (73). If instead the calculations are made using actual resource consumption recorded in the English UKPDS study, intensive polypharmacological glycaemic control is cost-saving (and hence a dominating alternative)\(^1\). Based on the UKPDS study a third economic analysis of intensive polypharmacological glycaemic control came to the result that the additional costs for intensified treatment and saved treatment costs as a result of fewer complications virtually balance out (636). The additional costs of intensive treatment are estimated at approx. GBP 48 per patient per year (approx. DKK 570). The difference between the costs for intensive and conventional treatment were not statistically significant\(^1\).

Intensive polypharmacological antihypertensive treatment

The cost-effectiveness of intensive polypharmacological antihypertensive treatment has also been analysed on the basis of UKPDS data. The additional costs for intensified antihypertensive treatment and saved treatment costs as a consequence of fewer complications virtually balance out (637). The additional costs for intensive treatment are estimated at approx. GBP 28 per patient per year (approx. DKK 330). The difference between the costs for intensive and conventional treatment was not statistically significant. Based on an estimate of the expected remaining lifetimes the costs per life-year for intensive antihypertensive treatment were estimated at GBP 720 (DKK 8,600). No effects of changes in quality of life were seen in the analysis. Neither the estimated difference in costs nor the estimated difference in lifetime were significantly different between the two interventions. The figures stated should be evaluated in the light of this. In an American model the cost-effectiveness ratio is estimated at USD \(-1,959\) (DKK \(-23,300\)) per quality-adjusted life-year, i.e. that intensive polypharmacological antihypertensive treatment is estimated to be cost-saving and hence a dominating alternative (73).

A precondition for the above conclusions is that complications are avoided and not just postponed. Whether or not this assumption holds is unknown.

Other economic analyses

Apart from the above-mentioned analyses of polypharmacological treatment, intensive glycaemic control with metformin has been shown to not only have positive effects on late complications, but also turns out to be cost-saving in overweight Type 2 diabetes patients (638, 639). Cholesterol-lowering treatment is estimated to cost between DKK 600 and 10,500 per life-year in diabetes patients with cardiovascular disease (640), between USD 4,000 and USD 40,000 (DKK 32,000-320,000) per life-year in diabetes patients without cardiovascular disease (641), and approx. USD 52,000 (DKK 420,000) per quality-adjusted life-year (73). The latter figure is based on model calculations, but as mentioned earlier it remains to be determined through randomised trials whether cholesterol-lowering drugs actually prevent atherosclerosis in all diabetes patients without cardiovascular disease.

How high costs society is willing to accept in order to gain one (quality-adjusted) life-year is ultimately a political decision. The cost-effectiveness ratios described above are not unusual in relation to other traditional treatment forms, however. Viewed in relation to screening for diabetes, intensive polypharmacological treatment seems to have a comparable or better cost-effectiveness ratio. Viewed in relation to screening for diabetic retinopathy, intensive polypharmacological treatment seems to have a comparable or poorer cost-effectiveness ratio.

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\(^1\) The cost differences are due among other things the costs for case management in the USA. In both cases the American units costs have been used.

\(^1\) A cost-effectiveness ratio is also calculated on the basis of the outcome measure “event free for 1 year”, c.f. Table 5.4.4.
<table>
<thead>
<tr>
<th>Study author</th>
<th>Aim</th>
<th>Method</th>
<th>Number &amp; country</th>
<th>Validated method</th>
<th>Results</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Eastman et al. 1997 (72) | To analyse the health and economic effects of treatment of Type 2 diabetes with the aim of achieving normal blood glucose levels (through intensive polypharmacy) | Model (Semi-Markov Monte Carlo simulation) | Hypothetical cohorts of 10,000 persons, aged 19-75 yr USA | Model design follows standard health economic principles | Costs per quality-adjusted life-year: USD 16,002. Cost-effectiveness ratio is better for young persons and particular ethnic groups. The results are sensitive to changes in the discounting rate and to changes in assumptions about the glycaemic regulation achieved under conventional (HbA1c 10%) and intensive treatment (HbA1c 7.2%) | • Effect-data from DCCT (Type 1)  
• No effect on CVD  
• Effect through HbA1c  
• Possible effects on quality of life associated with regular treatment not included |
| UKPDS 41 Gray et al. 2000 (690) | Estimate the cost-effectiveness of intensive glycaemic control versus conventional glycaemic control | Economic analysis based on randomised trial | 1,867 newly diagnosed Type 2 diabetes patients, average of 10 years follow-up UK | Economic analysis follows standard health economic principles. Unusual outcome measure (event-free years) | Intensive glycaemic regulation increases costs by GBP 476/patient/year. Incremental cost per event-free year with intensive glycaemic control GBP 166. Result is sensitive to assumptions about ‘real life’ resource consumption | Outcome measure for event-free years is difficult to interpret and does not reflect changes in quality of life with the various events. Based on assumptions about resource consumption in a real life situation. The results are probably sensitive to the discounting rate but this is not described |
| UKPDS 40 UK Prospective Diabetes Study Group 2000 (637) | Estimate the cost-effectiveness of intensive (tight) blood pressure regulation versus less intensive blood pressure regulation | Economic analysis based on randomised trial | 1,48 patients with Type 2 diabetes and raised blood pressure, average follow-up 8.4 years UK | Economic analysis follows standard health economic principles. One of the outcome measures is unusual though (event-free years) | Intensive blood pressure regulation increases the costs by GBP 237/patient/year. This corresponds to approx. GBP 28/patient/year. Incremental cost per event-free year with intensive blood pressure regulation GBP 149. Incremental cost per life-year with intensive blood pressure regulation GBP 720. Result is sensitive to assumptions about ‘real life’ resource consumption | Neither the estimated difference in costs nor the estimated difference in life years was significantly different for the two interventions. The figures stated should be viewed in the light of this. Changes in quality of life not included |
| CDC Diabetes Cost-effectiveness Group 2002 (73) | Estimate the cost-effectiveness of intensive glycaemic control, intensified blood pressure regulation and a reduction in cholesterol level | Markov-model | Model cohort of unspecified size Age 25 years and older USA | Model design follows standard health economic principles | Costs per quality-adjusted life-year: Intensive glycaemic control USD 4,184 (American resource consumption). Cost saving /dominating alternative (British resource consumption). Cost-effectiveness ratio for intensified glycaemic regulation is better for young persons and is sensitive to changes in the discounting rate. Intensified blood pressure regulation USD 1959 (i.e. cost saving /dominating alternative) Reduction in cholesterol level USD 5,089 | • Effect through HbA1c  
• Possible effects on quality of life associated with regular treatment not included |

20 Events are defined as: AMI, congestive heart failure, stroke, renal replacement therapy, amputation, cataract extraction, vitreous haemorrhage, death, any cause.  
21 Years without diabetes-related end-points (within the study period)
5.4.5 Subconclusions relating to the health economic aspects

- The total annual costs for regular control and pharmacological treatment of Type 2 diabetes patients in Denmark are estimated at just over DKK 0.5 billion.
- Implementation of intensive polypharmacological treatment of all Type 2 diabetes patients in Denmark can be expected to entail annual additional costs of between DKK 0.9 billion (realistic polypharmacy) and DKK 1.7 billion (systematic polypharmacy). In addition, this will necessitate start-up costs of DKK 7-18 million.
- Implementation of intensive polypharmacological treatment of Type 2 diabetes patients with microalbuminuria/albuminuria and/or coronary atherosclerosis can be expected to entail annual additional costs of between DKK 250 million (realistic polypharmacy) and DKK 630 million (systematic polypharmacy). In addition, this will necessitate start-up costs of DKK 7-18 million.
- There is no documentation for the cost effectiveness of concomitant intensive pharmacological treatment of several risk factors in Type 2 diabetes patients in Denmark. Foreign cost-effectiveness studies indicate that intensive polypharmacological glycaemic control can be cost saving or entail costs of up to DKK 300,000 per quality-adjusted-life-year. Intensive polypharmacological treatment of hypertension can be cost saving or have a cost-effectiveness ratio in the order of less than DKK 10,000 per life-year (not quality-adjusted). A precondition for these calculations of the cost-effectiveness ratio is that diabetic complications are avoided and not just postponed. Whether or not this assumption is valid is unknown.

5.5 Conclusions and recommendations

General

- Hypoglycaemic agents remove or attenuate symptoms such as diuresis, thirst, unintended weight loss and tiredness (2b).
- Hypoglycaemic agents reduce the frequency of late complications in the eye (1b), kidneys (1b) and peripheral nerves (2b). In order to avoid a single late diabetic complication, 20-50 Type 2 diabetes patients have to be treated with hypoglycaemic agents for 10 years. Typically, 1-2 different drugs have to be taken 1-3 times daily in tablet form (2b). Approximately half of the patients will eventually need to supplement tablet treatment with daily insulin injections in order to achieve good glycaemic control (1bF).
- Antihypertensive drugs reduce the risk of diabetic complications in the eyes (1b) and kidneys (1b), as well as the risk of atherosclerosis (1b). In order to hinder a single Type 2 diabetes patient developing serious cardiovascular disease, 6-15 people have to be treated with antihypertensive drugs for 10 years (1b). The risk reduction is greater the lower the blood pressure level achieved with treatment (1b). It is often necessary to use 3-4 different drugs administered 1-2 times daily in tablet form (1b).
- Cholesterol-lowering drugs prevent cases of cardiovascular disease in Type 2 diabetes patients with known atherosclerosis (1b). To avoid a single new case, 6-8 persons have to be treated for 10 years. In the case of Type 2 diabetes patients who are free of cardiovascular disease, it has not been finally clarified in randomised trials whether these drugs prevent atherosclerosis. However, observation studies (2b) clearly show an increasing risk with increasing cholesterol and change in the lipid composition of the blood – conditions that can be improved by treatment with cholesterol-lowering drugs. Treatment can usually consist of 1 drug administered once daily in tablet form.
- It is often necessary to use 5-8 drugs to ensure concomitant effective regulation of blood glucose, blood pressure and blood lipids.
- Pharmacological treatment reduces the risk of late complications of Type 2 diabetes. The individual patient and treating physician thus cannot know whether a given treatment will prevent late complications in the individual – only that the risk is reduced.
- It is not known whether late complications are prevented or just postponed by prophylactic treatment.
- It is not known how long death is postponed by a given prophylactic treatment.
- 50-70% of the Type 2 diabetes patients who have been prescribed tablet treatment take the tablets as prescribed (compliance). Compliance is greatest for tablets given 1-2 times daily (2b).
- All the treatments mentioned entail side effects (2b).
- Regarding hypoglycaemic agents, more comparative studies are needed to finally show which combination(s) of drugs within the drug group yield the most appropriate effect on morbidity and mortality. For the time being, though, treatment based on metformin should be preferred for overweight patients. As regards antihypertensive drugs, further comparative studies are needed to identify the most appropriate drugs and combinations of them.
- Clinical controlled trials are needed to elucidate the magnitude of the prophylactic effect of combining
many different drugs (polypharmacy). Similarly, information is needed on compliance, side effects and interactions when many drugs are prescribed simultaneously (polypharmacy).

- Compared with what is ideally attainable, pharmacological treatment of patients with Type 2 diabetes is not optimal in Denmark (2b). The introduction of systematic pharmacological treatment, including polypharmacy, therefore offers the possibility to reduce morbidity and mortality among Type 2 diabetes patients in Denmark.

Conclusions concerning special patient groups and polypharmacological treatment

- With cardiovascular disease, acetylsalicylic acid treatment protects against new thromboses. In Type 2 diabetes, approx. 25 persons have to be treated for 10 years to avoid one new case. It is unclear whether Type 2 diabetes patients without cardiovascular disease will benefit from acetylsalicylic acid treatment, but it should be considered if many risk factors for cardiovascular disease are present concomitantly. One tablet is given daily.

- If Type 2 diabetes is accompanied by cardiovascular disease, treatment with ACE inhibitors will protect against myocardial thrombosis, stroke and death, irrespective of the presence of hypertension and or albuminuria (1bF). According to the available RCT, approx. 7 patients have to be treated for 10 years to prevent one such event. Justifiable criticism has been raised against the study, however, and the effect can thus be smaller.

- Type 2 diabetes patients with microalbuminuria benefit from intensive lifestyle counselling in combination with polypharmacy (antidiabetic, antihypertensive and lipid-lowering drugs combined with acetylsalicylic acid). In order to prevent a single diabetic event, for example diabetic nephropathy or a single cardiovascular event, 2-3 persons have to be treated for 10 years (1b).

- In Type 2 diabetes patients with microalbuminuria and macroalbuminuria, antihypertensive treatment has a renoprotective effect independent of the starting blood pressure (1b). ACE inhibitors and angiotensin II receptor antagonists in particular should be preferred as the basic treatment because the renoprotective effect is greater than for other antihypertensive drugs. 10 years of treatment with the latter drugs can prevent 1 in 4 patients with microalbuminuria from developing nephropathy, and prevent 1 in 5-7 patients with nephropathy from developing renal failure. Treatment results in a decrease in albumin excretion. The greater the decrease, the better the renoprotective effect.

- All Type 2 diabetes patients should undergo an individual risk assessment as a basis for planning their non-pharmacological and pharmacological treatment (2b).

- Type 2 diabetes patients with atherosclerosis elsewhere than in the heart or with accumulated risk factors should be offered risk-reducing treatment pharmacological treatment (5).

- Type 2 diabetes patients with coronary atherosclerosis should be offered intensive polypharmacological treatment (1b).

- While it is feasible to carry out intensive polypharmacological treatment in highly specialised diabetes outpatient clinics under research conditions, knowledge of how and where the treatment can be most appropriately implemented in routine practice is lacking (1b).

- Structured diabetes care in general practice with the setting of individual treatment goals and systematic follow-up has positive effects on the risk profile in Type 2 diabetes (1b).

- Polypharmacological treatment encompasses several different drugs, and more knowledge is needed about the advantages and disadvantages of various types of treatment combinations (5).

Conclusions concerning the patient

- There is a distinct need for studies showing what information patients desire and need in order to be able to participate in the decision to initiate pharmacological treatment and in the regular adjustment of it.

- Studies are also needed of how to motivate patients to undergo permanent, often lifelong pharmacological treatment. Patients want full information concerning all treatment possibilities at the time the diagnosis is made (4), as well as information about how the disease and treatment will progress (4).

- Side effects associated with the use of a single drug are well known, whereas little is known about the frequency and type of side effects associated with the use of several drugs concomitantly (polypharmacy).

- Little is known about patient attitudes, quality of life and experience of treatment and side effects when prescribed many different drugs concomitantly (polypharmacy).

Conclusion concerning organisation

- Only sparse documentation is available regarding which organizational form in Denmark could best ensure that all diabetes patients receive good and uniform offers of pharmacological treatment (4).

- Diabetes care can be improved through the use of computers and databases to register the quality of the
diabetes care and to send out reminders to patients and physicians and through structured cooperation between the primary and the secondary sectors (1b).

- Patient education, individual goals and the inclusion of nurses in the diabetes care in general practice also seem to be able to improve the general treatment quality (1a). However, there is no documentation as to which professional groups can best take care of information, education, motivation for treatment and follow-up in relation to a more intensive use of drugs (1a).
- Little is known about what barriers exist within the organization and among healthcare professionals and patients as regards a more intensive use of drugs (2c).
- Intensive use of drugs requires structured further education of general practitioners and their staff as well as the allocation of resources to both the primary sector and the secondary sector (see economy section) (1b).
- There is a great need for health service research able to elucidate which organizational initiatives, including the use of polypharmacy, will improve diabetes care (4).

Conclusions concerning economy

- The total annual costs for regular control and pharmacological treatment of Type 2 diabetes patients in Denmark are estimated to be approx. DKK 0.5 billion.
- Implementation of intensive polypharmacological treatment of all Type 2 diabetes patients in Denmark can be expected to entail annual additional costs of between DKK 0.9 billion (realistic polypharmacy) and DKK 1.7 billion (systematic polypharmacy). In addition, this will necessitate start-up costs of DKK 7-18 million.
- Implementation of intensive polypharmacological treatment of Type 2 diabetes patients with microalbuminuria/albuminuria and/or a history of coronary atherosclerosis can be expected to entail annual additional costs of DKK 250 million (realistic polypharmacy) and DKK 630 million (systematic polypharmacy). In addition, this will necessitate start-up costs of DKK 7-18 million.
- There is no documentation for the cost effectiveness of concomitant intensive pharmacological treatment of several risk factors in Type 2 diabetes patients in Denmark. Foreign cost-effectiveness studies indicate that the costs of intensive polypharmacological glycaemic control can amount to over DKK 100,000 per quality-adjusted-life-year. Intensive polypharmacological treatment of hypertension can amount to under DKK 10,000 per life-year (not quality-adjusted). A precondition for these calculations of the cost-effectiveness ratio is that diabetic complications are avoided and not just postponed. Whether or not this assumption is valid is unknown.

Recommendations

- Glycaemic regulation should be intensified in Type 2 diabetes so that more patients attain a satisfactory blood glucose level. With the current pharmacological treatment possibilities this means that more patients should receive insulin treatment (A).
- The pharmacological treatment of hypertension in Type 2 diabetes should be intensified. In most cases this will entail treatment with several drugs (A).
- All Type 2 diabetes patients with atherosclerosis in the heart, brain and leg vessels should be offered intensive polypharmacological treatment consisting of acetylsalicylic acid, cholesterol-lowering statins and possibly also antihypertensive treatment based on an ACE inhibitor/angiotensin II receptor antagonist in accordance with the same criteria that apply to patients with coronary atherosclerosis (A+B).
- Type 2 diabetes patients who have developed complications in the form of albuminuria should be offered individualised intensive polypharmacological treatment consisting of acetylsalicylic acid, cholesterol-lowering statins and ACE inhibitor/angiotensin II receptor antagonist, possibly supplemented with anti-hypertensive treatment and hypoglycaemic agents (A).
- The remaining Type 2 diabetes patients should undergo regular risk assessment and on this basis should be offered treatment with a documented risk-lowering effect. Special attention should be paid to changes in the blood lipids in Type 2 diabetes (A).
- At the county level at least one organisation should be established to ensure coordinated, uniform and quality-assured implementation of evidence based non-pharmacological and pharmacological treatment that reduces morbidity and mortality among Type 2 diabetes patients (D).
6 Diagnosis and screening for late complications of Type 2 diabetes

6.1 Introduction and scope

6.1.1 Late complications of Type 2 diabetes

In time, the dysmetabolic state that occurs in Type 2 diabetes can cause late complications in the form of damage to the blood vessels and nervous system. The negative consequences of these late complications can be prevented and limited by optimal regulation of blood pressure and blood glucose (addressed in the preceding chapter), but also depend on the duration of the diabetes. Type 2 diabetes is not usually diagnosed until several years after the onset of disease. Not infrequently, therefore, it is detection of a late complication that leads to recognition that the patient has diabetes. Late complications are generally rarer in Type 2 diabetes than in Type 1 diabetes. As the number of patients with Type 2 diabetes is far greater, however, they account for approx. half of the total number of diabetes-related complications.

6.1.2 Scope

The medical interventions against late diabetic complications encompass prevention, case finding, diagnosis, treatment and rehabilitation. With late diabetic complications, the diagnostic process is closely associated with screening. Thus diagnosis and screening of these complications can advantageously be subjected to a health technology assessment together. With all late complications of Type 2 diabetes, both the type and principles of treatment and rehabilitation are well documented and vary little throughout the world. As a consequence, these will be defined as fixed values for each late complication and not be included as variables in the analysis.

This chapter will therefore be restricted to screening and diagnosis of late complications in Type 2 diabetes. These late complications encompass:

- Diabetic retinopathy
- Diabetic nephropathy
- Diabetic neuropathy
- The diabetic foot
- Cardiovascular disease (atherosclerosis).

6.2 Technology

6.2.1 Retinopathy

Morbidity

The eye can be roughly compared with a camera – at the front there is an optical system (the cornea, the pupil and the lens), in the centre a camera housing (the vitreous body) and at the back a photographic film (the retina). All the components of the eye are affected by diabetes, but most of these effects do not pose any real threat to the sight, and they can be treated without complication, e.g. operation of diabetes-related cataract.

The chief reason diabetes poses a threat to the sight is the damage that can occur in the retina, i.e. diabetic retinopathy. Diabetic retinopathy is characterised by a number of different lesions, all of which can be ascribed to disruption to the retinal blood supply (haemorrhage, exudation of albumin from the blood vessels, oedema and a number of vessel abnormalities). These changes start in the periphery of the retina and can develop into two sight-threatening forms, namely proliferative diabetic retinopathy and diabetic maculopathy. With diabetic maculopathy, the changes spread towards the central parts of the retina where they cause direct damage to the vision. With proliferative diabetic retinopathy, new blood vessels proliferate to substitute for the occluded blood vessels in the periphery of the eye. The new blood vessels are structurally abnormal, however, causing haemorrhage into the vitreous body or retinal detachment, both of which severely affect the sight. Diabetic retinopathy is not detected by the patient himself in the early stages, when the changes have not impaired the sight. However, systematic case finding of asymptomatic changes enables permanent impairment of the sight to be prevented and treated effectively.

Both of these sight-threatening complications, i.e. proliferative diabetic retinopathy and diabetic maculopathy, can be treated using lasers, in both cases reducing the risk of loss of sight by 50% (642) (1a) (643) (1a).
What is screening and treatment intended to prevent?
The goal of screening for diabetic retinopathy is to prevent loss of sight defined as the occurrence of the following:

- “Social blindness”, defined as a fall in visual acuity to under 0.1 as a consequence of diabetic retinopathy
- “Partial-sightedness”, defined as a fall in visual acuity to a level below normal, but not to social blindness. In Denmark, this corresponds to a visual acuity of between 0.1 and 0.3.

Prevalence of the complication

Retinopathy

No studies are yet available describing the prevalence of retinopathy in an unselected population of patients with Type 2 diabetes. The available data derive from populations who participate in screening programmes or who have been referred to an ophthalmologist and who can therefore be presumed to have a higher prevalence of retinopathy than the general population. A common feature of the existing studies, however, is that a considerable proportion of the patients (8.7-46%) already have retinopathy at the time the diabetes is diagnosed (644) (1b) (645) (1a) (646) (1b) (647) (1b) (648) (1b). At the time of diagnosis, 0-4% have treatment-requiring proliferative retinopathy (648) (1b) (645) (1a) and 0-7% have treatment-requiring maculopathy (645) (1a) (646) (1b).

After the time of diagnosis, the average annual incidence of retinopathy of any degree is reported to be between 1.8 and 2% over 25 years (645) (1a) (649) (1a) and between 2.5 and 4.5% during the first 10 years (648) (1b) (645, 649) (1a) (644) (1b) (647) (1b).

The average annual incidence of proliferative diabetic retinopathy has been found to be 0.8% over 25 years from the time of diagnosis (645) (1a) (649), although an average incidence of 1.4% over 4 years has been reported for a population-based cohort (647) (1b).

The average annual incidence of diabetic maculopathy has been found to be between 0.5 and 0.6% from the time of diagnosis and over the following 25 years (171) (1a) (175) (1a).

Partial-sightedness

At the time of diagnosis the annual incidence of diabetes-related partial-sightedness is 5% with an average of 0.2% the first 5 years and 1.2% the following 5 years (648) (1b). The prevalence of diabetes-related partial-sightedness in the Type 2 diabetes population is reported to be 7% while that of social blindness is 1.1 and 1.6%, respectively (650) (1b) (649) (1b). In a screening programme the population-based 4-year incidence was 1.7% for partial-sightedness and 0.5% for social blindness (650) (1b).

Standard treatment

The treatment consists of laser photocoagulation of the retina and can improve the prognosis by at least 50% in both proliferative diabetic retinopathy and diabetic maculopathy (651) (1a).

- With proliferative diabetic retinopathy, laser treatment is performed on the whole of the periphery of the retina outside the blood vessels that arch around the yellow spot (panretinal photocoagulation). In advanced cases with haemorrhage into the vitreous body and retinal detachment due to traction, the standard treatment is vitrectomy.
- With diabetic maculopathy, laser treatment is performed in a grid pattern, or in a localised area (focally) corresponding to the area of the retina that is oedematous and which is located more than 400 micrometres from the area where the retina is fixed (central fovea).

Nature of the technology

Screening for diabetic retinopathy can be performed by ophthalmoscopy, which is direct observation of the retina through the pupil of the eye with the use of an ophthalmoscope. The examination can also be performed by fundus photography whereby any changes are documented on photographic or digital media. In most places in Europe it is common to also measure visual acuity, but the independent value of this examination for detecting sight-threatening changes has not been clarified. However, visual acuity is always used to estimate the visual consequences of diabetic retinopathy.

The literature about screening for diabetic retinopathy is comprehensive for Type 1 diabetes, but this can only be partly transferred to Type 2 diabetes as the patients are generally older than Type 1 diabetes patients.
and hence have more age-related changes in the lens of the eye, e.g. cataract, which can veil and distort the appearance of the retina. Moreover, the distribution of the retinal lesions seen in Type 2 diabetes patients with retinopathy differs from that seen in Type 1 diabetes patients.

Who should be screened?
As all diabetes patients are at risk of developing diabetic retinopathy it is standard practice to recommend regular screening of the whole of the diabetes population. In principle, the examination should answer the following two questions:

1) Are there treatment-requiring changes (proliferative diabetic retinopathy or diabetic maculopathy) necessitating that the patient should be referred to closer examination or treatment at a specialist department?
2) If not – how serious is the retinopathy, and how is it used to define the optimal time interval until the next check-up?

How good is the screening method?
Screening for diabetic retinopathy can be performed in two principally different ways, i.e. by ophthalmoscopy and by fundus photography. Comparative studies of ophthalmoscopy and fundus photography in Type 2 diabetes have shown that the two methods can be equally good at identifying treatment-requiring changes (652) (1a) (653) (2b), but that the ophthalmoscopy then has to be undertaken by a person experienced in the examination, preferably an ophthalmologist (654) (2b) (655) (656) (657) (2b). Moreover, an ophthalmologist will have the possibility to perform supplementary examination with special equipment if necessary (658) (2b) (659) (2b), e.g. for the demonstration of exudation at the area of acute vision (659) (2b). Even with experienced ophthalmologists, however, there is an up to 50% risk of overlooking the very earliest changes by ophthalmoscopy and hence of making an incorrect recommendation as to the interval to the next check-up (660) (2b).

Photographic documentation of changes provides a further possibility to ensure quality assurance and to estimate minor changes in the degree of retinopathy from examination to examination. Moreover, photographic documentation is a precondition for repeated evaluation of the changes with participation of several specialists. These aspects have not been subjected to a further investigation, however.

Under optimal conditions with fundus photography on a medium with a high resolution and subsequent evaluation by a trained grader the sensitivity and specificity of the method is close to 100% for detecting both the earliest changes that define the check-up interval and treatment-requiring changes, while exudation is more difficult to detect on the basis of photographs alone (656) (2b) (658) (2b) (653) (2b). Fundus photography can be performed using different types of camera and different kinds of technique (stereo, non-mydriatic, black/white, angiography). There is no evidence that the quality of these methods differs provided two conditions are met. Firstly, the photograph must encompass the relevant parts of the retina (661) (2b) (659) (2b) (662) (2b), and secondly, the resolution of the film or digital medium has to be sufficient to visualise the smallest changes (663) (2b) (664) (2b).

What is the optimal extent and frequency of screening?
The evidence indicating the optimal screening interval for retinopathy in Type 2 diabetes is poor. It is agreed that screening should be initiated at the time of diagnosis and, inspired by the recommendations for Type 1 diabetes, many specialists choose to thereafter perform annual screening. A few studies suggest that this general recommendation should be modified, however. Thus, while it is cost-effective to screen younger persons with poor regulation annually, older persons with good regulation can be screened less often (665) (1b) (666) (1b). If little or no retinopathy is detected at the time the diabetes is diagnosed and provided blood glucose and blood pressure are kept well-regulated, the next check-up can wait until after 4 years (667) (2b). Effectiveness of screening for diabetic retinopathy
The usefulness of screening for diabetic retinopathy is so well established (668) (1a) that based on present knowledge it is considered unethical to refrain from screening if screening is possible. As a consequence, there are no systematic studies with a high level of evidence comparing screening versus no screening for diabetic retinopathy in Type 2 diabetes.
Risks
The application of eye drops can induce allergic conjunctivitis (due to the presence of preservatives) or acute glaucoma. These complications are rare, however, and can easily be treated.

Subconclusion

- Sight-threatening diabetic retinopathy can be identified by screening (1a) and can subsequently be treated by laser treatment, which reduces loss of sight by at least 50% (1a).
- Screening can be performed by ophthalmoscopy or fundus photography. The latter method is best at detecting the earliest changes (2b).
- The evidence suggests that screening for retinopathy should be carried out from the time Type 2 diabetes is diagnosed and the check-up interval thereafter adjusted to the severity of the retinopathy. Evidence suggests that younger, poorly regulated patients should be screened annually. Elderly persons with newly arisen diabetes can be screened less frequently – as long as 4 years after the first examination if the result is normal. A precondition, though, is an acceptable, unchanged metabolic status (1b).

6.2.2 Nephropathy/hypertension

Morbidity and prevalence of the complication
Diabetic nephropathy, defined as the presence of permanently raised albumin excretion in the urine (24-hour albumin >300 mg; at least two out of three urine tests) and concomitant diabetic retinopathy (669), develops in approx. 40% of all patients with Type 2 diabetes (670) (2b). The development of nephropathy in Type 2 diabetes patients is prognostically closely associated with increased mortality from cardiovascular disease (671) (2b).

The percentage of Type 2 diabetes patients who develop end-stage renal failure (ESRF) is relatively low (4-8%) (672) (2b) compared with the corresponding figure (30-35% in Type 1 diabetes patients (673) (2b). Due to the large number of Type 2 diabetes patients, however, impaired renal function and the treatment of ESRF quantitatively comprise a major problem entailing considerable socioeconomic costs. According to the Danish Society of Nephrology (www.nephrology.dk), diabetes patients accounted for 22% of all patients under dialysis in Denmark in 2001 (of which half had Type 2 diabetes), and the percentage has steadily increased during the past two decades. In the USA, 44% of patients with newly diagnosed ESRF have diabetes.

Hypertension is present in approx. half of patients at the time the diabetes is diagnosed (674) (2b) and develops in the majority of the remainder during the course of the disease (669). The development of hypertension is also partly associated with the development and progression of microalbuminuria (urine albumin excretion >20 microgram/min) and partly due to the fact that microalbuminuria is very strongly associated with increased cardiovascular morbidity and mortality (671).

Patients with albuminuria and Type 2 diabetes are a pathophysiologically and pathoanatomically far more heterogeneous group than is the case for patients with Type 1 diabetes. In many cases, albuminuria in Type 2 diabetes patients is thus attributable to causes other than diabetic nephropathy (up to 30%). The clinical course of nephropathy in Type 2 diabetes patients in many ways resembles that in Type 1 diabetes patients, however, entailing progressively increasing albumin excretion, hypertension and increasingly impaired renal function (675) (2b) (676) (2b). Moreover, it has been shown that the rate at which renal function diminishes is closely related to the degree of hypertension (676) (2b).

Standard treatment
Early and aggressive treatment of hypertension is central to the care of patients with Type 2 diabetes. The treatment goal is lower (135/85) for diabetes patients than for other patient groups (2), and the WHO and the American Diabetes Association (ADA) have recently reduced this even further (<130/80). Optimisation of metabolic regulation, exercise, weight loss and reduced dietary salt intake are appropriate – but rarely adequate – treatment elements. Pharmacological therapy with several different antihypertensive drugs is often necessary, as is also discussed in Chapter 5.

Regular monitoring of blood pressure and urine albumin excretion therefore go hand in hand in the care of Type 2 diabetes patients.

Effective treatment of hypertension has a documented effect on the progression of renal disease as judged from the albumin excretion, as well as on total mortality and – in particular – on mortality from cardiovascular disease (558) (1b) (553) (1b) (581) (1b).
It has recently been shown that in patients with Type 2 diabetes and microalbuminuria or manifest diabetic nephropathy, pharmacological blockade of the renin-angiotensin system hinders progression of the diabetic nephropathy as judged from urine albumin excretion – apparently independently of the effect on the blood pressure (578) (1b) (579) (2b) (580) (2b).

**Nature of the technology**

**Blood pressure**

Blood pressure can be measured by:

A) Ambulatory blood pressure monitoring, either auscultatory, i.e. in the traditional manner with a mercury manometer, or oscillatory, using various automatic devices

B) Self-monitoring (carried out by the patient himself with automatic devices)

C) 24-hr blood pressure measurement with automatic devices.

There is reason to advise against some of the non-validated automatic devices, which can make very imprecise measurements. An updated list of validated blood pressure monitors can be found on the British Hypertension Society website [http://www.hyp.ac.uk/bhs/bp_monitors/resources.htm](http://www.hyp.ac.uk/bhs/bp_monitors/resources.htm). In general, wrist monitors should be avoided. The Danish Hypertension Society has published a guidance report on both 24-hour blood pressure measurement and self-monitoring.

There is no evidence indicating how often blood pressure should be measured for screening purposes in Type 2 diabetes, however. For pragmatic reasons, it is recommended to check ambulatory blood pressure at least once a year. With blood pressure >140/90, the measurements should be repeated with a view to intervention. “White coat hypertension” is a well-described reason for falsely raised blood pressure (677) (1a). If resources and possibilities are available, hypertension verification in the form of 24-hour blood pressure monitoring can be considered.

**Urine albumin:** Screening for albuminuria can be carried out in different ways:

1) Determination of albumin by means of laboratory-based assays. When the length of the sampling period is known, the albuminuria is expressed as an excretion rate (e.g. microgram/min, mg/day or micromole/day)

2) Estimation of the concentration by means of high-sensitivity semi-quantitative test strips

3) Determination of the ratio between urine albumin and urine creatinine (albumin/creatinine ratio) in a small urine sample.

These methods have been investigated in several large comparative studies of populations of patients with Type 1 diabetes, and in a single study of Type 2 diabetes patients (678) (1a). The latter study recommended the use of morning urine and determination of the albumin/creatinine ratio in three morning urine samples (678). Spot urine sampled at other times of the day is usually advised against (679, 680).

The advantages and disadvantages of the methods differ. The test strip method is the most expensive, while determination of albumin/creatinine ratio is more accurate in that it eliminates the uncertainty associated with urine collection.

**Who should be screened?**

As all diabetes patients are at risk of developing diabetic nephropathy, the usual practice is to recommend regular screening of the whole diabetes population.

**What is screening and treatment intended to prevent?**

Symptomatic kidney disease.

Mortality from cardiovascular disease.

**How good is the screening method?**

Clinical diabetic nephropathy is defined as raised urine albumin measured using one of the common methods described above. The factor screened for is the presence of microalbuminuria – the specificity depends on the population, and false positive screening results are seen in urinary infection.

Hypertension is virtually always detected by standard measurement of ambulatory blood pressure. The speci-
ficity is lower, however, due to the risk of “white coat hypertension”. These cases can be revealed by 24-hour blood pressure monitoring.

**What is the optimal extent and frequency of screening?**

As mentioned above, there are no studies indicating how often – and at what intervals – blood pressure and urine albumin should be measured for screening purposes. With patients with normal blood pressure and normal urine albumin the consensus is screening at least once per year.

**Efficacy of screening for diabetic nephropathy**

There are no studies clarifying the effect of screening on ESRF or cardiovascular disease. As screening can improve the prognosis of the early stages of these complications it is commonly believed that screening must also limit the occurrence of severe renal and cardiovascular complications.

**Subconclusion**

- Diabetic nephropathy is preceded by an asymptomatic period of albuminuria and progressive hypertension (1b).
- Diabetic nephropathy can potentially be prevented by early initiation of treatment with antihypertensive drugs (1b).
- Screening for albuminuria and hypertension should be carried out annually in the whole population of diabetes patients (4).
- There are no studies clarifying the effect of screening per se on end-stage renal failure or on cardiovascular disease.

**6.2.3 Neuropathy**

**Morbidity and frequency of complications**

*Peripheral sensorimotor polyneuropathy:* Diabetics can cause degeneration of peripheral nerves, resulting in degeneration of the nerve fibres (axonal degeneration) and partial loss of the nerve sheath (segmental demyelination). In the course of time, this will cause dysfunction of both sensory and motor function. Clinically, this is identified by the inability to provoke tendon reflexes, and slow loss of sensory functions. With more severe degrees of neuropathy the motor system is also affected, with loss of muscle tissue starting at the feet, but possibly spreading up the legs.

At the time of diagnosis, 8% of Type 2 diabetes patients have polyneuropathy defined on the basis of tendon reflexes and neurophysiological investigations (681) (2b). After approx. 10 years of diabetes, 25-40% develop polyneuropathy (682) (1b) (683) (4) (683) (4).

*Erectile dysfunction:* Men with Type 2 diabetes more frequently have erectile dysfunction than men in general. The complaints typically consist of reduced ability to have and maintain an erection and of retrograde ejaculation. The reported prevalence of erectile dysfunction in Type 2 diabetes patients varies markedly from 23 to 89% (684) (2c) (685) (4) (686) (4). Erectile dysfunction can be caused by neurogenic, vascular and psychogenic factors and is related to poor glycaemic regulation, peripheral and autonomic neuropathy and macroangiopathy.

**Standard treatment**

*Loss of sensation:* There is no known treatment for loss of peripheral sensation. With improved glycaemic regulation it is possible to reduce the risk of development and progression of peripheral sensorimotor neuropathy, probably including loss of sensation. These experiences have primarily been obtained in studies of Type 1 diabetes mellitus patients (the DCCT study), but similar conditions probably apply for Type 2 diabetes (540) (1b). With loss of sensation, prevention of foot ulceration is very important (see Section 6.2.4).

*Erectile dysfunction:* Per oral treatment with a phosphodiesterase inhibitor has an effect in approx. 50% of patients with diabetes compared with a placebo effect of 10-15% (687) (1b). Apomorphine has recently proven to be effective in erectile dysfunction, but the effect in diabetes patients has not been investigated. If treatment with a phosphodiesterase inhibitor is contraindicated, intracavernous injections of papaverine or implantation of a penile prosthesis can be effective (688) (2b) (689) (4).
**Nature of the technology**

Loss of sensation: Clinical examination of sensation and the deep tendon reflexes on the lower extremities. Quantification of sensation using a monofilament and determination of the vibration perception threshold. For details see Section 6.2.4.

Erectile dysfunction: Questionnaire for evaluating the degree of erectile dysfunction (690) (4). Methods for characterising erectile function have been developed, but never systematically utilised on a large scale.

**Indications for screening**

As all diabetes patients are at risk of developing neuropathy, standard practice is to recommend screening of the whole diabetes population.

Experience of screening for erectile dysfunction among diabetes patients is sparse. At present there is thus no evidence for implementing a screening programme.

For information regarding outcome parameters and quality, extent, effectiveness and risks associated with screening, see Section 6.2.4.

**Subconclusion**

- Approximately 8% of Type 2 diabetes patients have polyneuropathy in the form of loss of peripheral sensation or erectile dysfunction at the time the diabetes is diagnosed, and approx. 25-40% after 10 years of the disease (1b).
- As all diabetes patients are at risk of developing neuropathy, the standard practice is to recommend screening of the whole diabetes population (see Section 6.2.4). There is no evidence to support the implementation of screening programmes for erectile dysfunction.

**6.2.4 The diabetic foot**

**Morbidity**

Foot complications in diabetes encompass 1) foot ulceration, often complicated by infection and gangrene, which can lead to 2) amputation and hence possibly loss of mobility. A further complication is 3) foot deformities (Charcot foot), with persistent and possibly permanent loss of mobility and increased risk of foot ulceration and amputation.

**Foot ulceration**

Ulcers on the feet arise as a consequence of a complex of late complications encompassing:

- Peripheral neuropathy (degeneration of the nerves, especially in the feet)
- Structural changes to the connective tissue, which cause stiff joints
- Increased susceptibility to infection
- Atherosclerosis with reduced blood flow (possibly even gangrene).

Peripheral polyneuropathy leads to changed sensitivity to pain, pressure, touch and temperature, i.e. changes to the warning system that normal protects against bruises, pressure and wear damage, burns, etc. As a consequence, even serious conditions that normally cause pain and other discomfort can arise and spread without them being noticed by the patient. The weakening of the nerve supply also affects the muscles of the feet and legs. This, together with structural connective tissue changes, leads to stiff joints, bunions/corns, hammer toes and other deformities such that the foot becomes more susceptible to damaging pressure with resultant calluses, blisters and ulcers. The autonomic neuropathy affects regulation of the blood flow and causes perspiration to diminish or cease. As a result the skin dries out, leading to the formation of cracks and fissures, and eventually to ulceration.

**Amputation**

Diabetes increases the susceptibility to infection. At the same time, the usual symptoms of infection are often mild such that the infection can become very widespread and serious before it is detected. The atherosclerosis that often accompanies diabetes affects the blood flow, which can lead to ulceration and/or gangrene. Both infection and gangrene entail the risk of amputation – at best, minor amputations to the toes of foot, at worst, amputation of the leg. The healing of foot ulcers is slow in neuritis and impaired circulation and may even be cease completely, with the risk that the ulcers can become chronic or necessitate amputation.
Charcot foot
Development of Charcot foot is due to collapse of the foot bones and joints, and begins with spontaneous fractures in architecture of the foot. A foot deformity usually develops, and there is a risk of recurrence and an enhanced risk of foot ulceration.

Frequency of complications

Foot ulceration
In the combined Type 1 and Type 2 diabetes population the incidence of foot ulcers is 2.2-5.9% (691) (5), while that for Type 2 diabetes in Sweden is 3.6% (692) (3b). The prevalence is reported to be between 3 and 8% (693) (3a) (692) (3b). In a Danish review of inner Copenhagen patients the prevalence of manifest foot ulcers was 6.4% (9% in at-risk patients), while that of previous foot ulcers was 24% (694) (3b). The prevalence was higher among patients with Type 2 diabetes than among patients with Type 1 diabetes. Moreover, a mixed diabetes population with foot ulcers and incipient or manifest gangrene typically includes more patients with Type 2 diabetes than with Type 1 diabetes (695) (3b).

Charcot foot
A somewhat rarer complication is the Charcot foot. The incidence among diabetes patients (mixed Type 1 and Type 2) reportedly ranges from 0.08 to 7%, and was 0.3% in a Danish population (696) (3b). Among these patients the annual risk of reversion to treatment-requiring changes is approx. 9%, while that of foot ulceration is 17% (697) (3b).

Amputation
On the foot: The annual incidence is reported to be 3-6 per 100,000 persons, or 1.2-3.4% per 1,000 patients with diabetes (698) (2b). The prevalence is 0.7-4% (699) (3b) (700) (2b). In a cohort from Copenhagen, the prevalence was 4.7% (694) (3b).

Leg amputation: The annual incidence varies from 3.6 to 20.5 per 100,000 persons (698) (2a), corresponding to 0.018 to 0.4% of diabetes patients given a diabetes prevalence of 5%. Moreover, diabetes patients account for 30-60% of all leg amputations (698) (2a), corresponding to 5-15 times the expected number – in other words diabetes patients are considerably overrepresented. The prevalence of leg amputation reportedly ranges from 0 to 2% (699) (3b) (701) (2b). In the Danish cohort the prevalence was 0.4% (694) (3b).

Standard treatment
An international consensus report (691) (5) recommends that treatment of diabetic foot problems should be managed by a multidisciplinary team – typically consisting of a diabetologist, a specially trained nurse, a podiatrist, an orthopaedic surgeon, a cardiovascular surgeon, orthopaedic shoemaker and an orthotist. Smaller teams can take care of most of the tasks, but there has to be access to a full centralised, multidisciplinary team, possibly integrated in a wound centre. Patients with foot ulcers or Charcot foot should thus be referred to a diabetic foot team or wound centre with a view to diagnosis and treatment. See also Chapter 4: “Non-pharmacological treatment of Type 2 diabetes”.

Nature of the technology
Screening comprises clinical examination of the feet. The examination should clarify whether there are risk factors for the development of ulcers or Charcot foot, i.e. a complex clinical examination of the feet for:

- Skin and nail changes
- Foot deformities
- Circulatory disturbances by pulse palpitation and possibly measurement of ankle blood pressure.

In addition, sensation is tested with a monofilament (ability to feel a nylon thread that flexes at a pressure of 10 grams), and age, type and duration of diabetes, and a history of foot ulcers or amputation are registered.

In patients identified by screening as being at risk of foot ulceration, a complex of prophylactic measures is initiated depending on the findings. See Chapter 4 “Non-pharmacological treatment of Type 2 diabetes”. It is not presently possible to screen specifically for risk factors for Charcot foot. However, the detection of neuropathy indicates that there is a risk of both foot ulceration and Charcot foot, with the risk of foot ulceration being 10-20-fold greater than for Charcot foot.
Who should be screened?
As all diabetes patients are at risk of developing foot ulcers, and as this risk increases with time, standard practice is to recommend screening of the whole diabetes population.

What are screening and treatment intended to prevent?
- Foot ulcers (newly arisen and recurrent)
- Foot infection
- Amputation on the foot and leg
- Charcot foot.

How good is the screening method?
The effectiveness as regards identifying at-risk feet has been investigated in three prospective studies. In one of the studies (702) (3b), in which neuropathy was examined for using a Semmes-Weinstein 10-g monofilament (703) (2b), the sensitivity and the specificity for predicting ulceration were 93 and 86%, respectively. The risk of ulceration was 5-fold higher in the group with loss of sensation than that in the group with intact sensation. In the other two studies a biothesiometer was used to measure neuropathy and in the first of these studies, sensitivity was 83% and specificity was 62% (704) (3b).

Neuropathy also be tested for using a tuning fork, temperature sensibility registration and other methods, but these have not been investigated in prospective studies as is the case for the biothesiometry and monofilament methods. Direct comparisons between these two methods have been made, but no difference has been found (703) (5b). Reproducibility studies of biothesiometer, monofilament and pulse palpation (706) (3b) have shown satisfactory results for the monofilament. Moreover, the examination is cheap and easy to perform, the monofilament can be kept in the pocket, and it does not require an electric current (703) (2b). There is no evidence that supplementing pulse palpitation with measurement of ankle or toe pressure improves the screening examination.

Although reproducibility and uncertainty remain to be clarified for most of the variables included in screening programmes, simple screening programmes employing the monofilament or biothesiometer methods to identify neuropathy have nevertheless proven effective with respect to identifying at-risk feet (702, 705) (3b).

What is the optimal extent and frequency of screening?
There are no studies indicating a single optimal screening programme (see the section above), and no investigations have been made that clarify what the optimal screening interval should be. However, there is clinical consensus in favour of annual screening (497, 691-706) (5). As mentioned earlier, the purpose of screening is to identify patients at high risk of foot ulceration so that these high-risk patients can be offered prophylactic treatment to reduce the risk of foot ulceration and amputation (491) (2b) (493) (1b) (494) (3b).

Who should perform the screening?
There are no studies comparing the primary and the secondary sectors as regards screening, but the overall care of feet has been examined in several studies. See Chapter 4.

What is the risk associated with screening?
This is presumably low, especially seen in relation to the considerable benefits.

Subconclusion
- The aim of screening for diabetic foot problems is to identify patients at risk of future ulceration and amputation. In such patients, education and treatment can reduce the frequency of amputation (1b).
- The diabetes patient’s foot problems encompass diabetic foot ulcers, amputations and abnormal posture.
- These problems are often preceded by a period of loss of sensation and increasingly impaired blood flow to the feet.
- The loss of sensation is most easily and precisely measured using a monofilament test (2b).
- It has been shown that monofilament testing has a high sensitivity and specificity for predicting subsequent foot problems (3b).
- There are no studies documenting how frequent the screening should be, but the general consensus is that it should be annual (4).
- Neither are there studies documenting which part of the health system should carry out the screening.
6.2.5 Diabetic cardiovascular disease

Diabetic cardiovascular disease encompasses a history of often more diffuse atherosclerosis than that seen in patients without diabetes, as well as an increased risk of sudden unexpected death. Atherosclerosis of the coronary arteries can cause angina pectoris, myocardial infarction and heart failure. Sudden unexpected death is presumed to be due mainly to cardiac arrest in connection with myocardial infarction or arrhythmia. Atherosclerosis in the brain causes cerebral infarcts or recurrent transient cerebral ischaemia. Atherosclerosis in the legs can give rise to walking pains (claudicatio), foot ulcers and gangrene. Moreover, the changed glucose metabolism in diabetes causes increased stiffness of the large vessels that plays an as yet unresolved role in heart failure and impaired blood flow to the legs. This aspect is consequently not addressed further here.

As mentioned in Chapters 4 and 5, age, male gender, smoking, high blood lipid levels, hypertension, high blood glucose and albuminuria are the traditional risk factors for the occurrence and progression of cardiovascular disease in Type 2 diabetes. If the patient has developed symptomatic or clinically demonstrable cardiovascular disease, all the identified risk factors should be treated (Chapter 5). If there is no immediately demonstrable cardiovascular disease, these risk factors should be monitored and treated if the patient’s risk can thereby be reduced.

As the degree of atherosclerosis in for example the leg vessels and coronary arteries is closely correlated, impaired blood flow to the legs is an important risk factor for heart disease. Changes in the carotid arteries judged by ultrasound are also a risk factor for heart disease (see below).

In order to ensure that prevention is initiated as early as possible and to delay the progression of atherosclerosis, as well as to if possible prevent it causing thrombosis and premature death, intense efforts have been made within the past decade to identify new and possibly more specific risk factors and markers for cardiovascular disease.

These encompass biochemical changes in the blood that affect the coagulation of the blood (platelet function, fibrinolysis), substances produced by the innermost layer of the vessel walls (endothelin, PAI-1), the ability of the arteries to dilate (flow-mediated products), arterial elasticity (arterial compliance), signs of activation of a biochemical inflammation (C-reactive protein), and the protein homocystein. All these factors are associated with cardiovascular disease, but no single factor alone provides a better risk assessment than the traditional risk factors. A combination of new (e.g. C-reactive protein) and traditional risk factors might possibly enhance the strength of the risk assessment.

Apart from the case history and the medical examination there are various vascular investigations and tests able to diagnose manifest atherosclerotic diseases and in certain cases to reveal their asymptomatic initial stages (subclinical). The impact on morbidity and mortality in Type 2 diabetes of such screening for clinical and subclinical cardiovascular disease has not been studied. Thus there is no evidence indicating in what manner and how frequently screening for cardiovascular disease in Type 2 diabetes should be performed. Due to the magnitude and severity of the problem (see Chapter 5), the value of these tests in the diagnosis of treatment-requiring atherosclerosis and the assessment of the degree of atherosclerosis will be addressed below focusing particularly on subclinical heart disease.

Diabetic heart disease

It is claimed that the electrocardiograms of diabetes patients more frequently show signs of asymptomatic myocardial ischaemia at rest and during physical stress than those of individuals without diabetes (707). The significance of this so-called silent myocardial ischaemia has not been clarified, but naturally enough has been linked to the more frequent occurrence of cardiovascular disease and sudden death. Among diabetes patients, moreover, permanent changes are frequently found in the electrocardiogram indicating a history of asymptomatic coronary thrombosis. This has been attributed to late diabetic complications in the nerve supply to the inner organs (autonomic neuropathy) that prevent the heart pains from being felt, but this has only been partly substantiated scientifically (707). Consequently, heart disease has often developed before it has been possible to initiate prophylactic treatment. A screening method that can ensure earlier diagnosis and hence treatment of coronary atherosclerosis can therefore be expected to improve the prognosis of diabetes patients. This applies to both intensive treatment of risk factors, anti-coagulation therapy and by-pass surgery. In contrast, the value of balloon dilatation in diabetes remains to be clarified. When the diabetes patient has a myocardial infarct, the prognosis is poorer than for the patient without diabetes. More patients die before they get to the hospital, and more also die thereafter. It would therefore be useful to identify patients at high risk of developing coronary thrombosis.
Coronary angiography – CAG. A so-called invasive investigation of the coronary arteries in which a catheter is inserted into the blood stream and a contrast medium is injected into the coronary arteries. This can ensure a diagnosis, but is not without risk and is expensive. It is therefore neither ethical nor realistic from the resource point of view to use CAG to screen large groups of Type 2 diabetes patients devoid of symptoms or signs of heart disease.

Electrocardiogram at rest. A universally available, easy and cheap method, but one that does not provide a sufficiently certain diagnosis of atherosclerosis and certainly not of the degree of the latter. There are too many uncertain (e.g. at heart block), false negative (only ischaemia during stress) and false positive results (e.g. in hypertension) (708). Only a certain positive result (changes after previous myocardial infarct) is useful. The consequence of this is pharmacological treatment of the risk factors while – unlike in the USA (709) – there is no European consensus as to the further diagnosis with a view to treating narrowing of the coronary arteries, as outlined below.

Electrocardiogram under physical stress (stress testing with ECG). This is the traditional universally accessible test that can reveal relative myocardial ischaemia due to narrowing of the coronary arteries. When heart disease is suspected this is presently the primary test in Denmark. The test has been standardised as to which stress (bicycle or treadmill) should be imposed in the form of a pulse increase in order for the test to be certain. In this situation there will often be limitations for the diabetes patient in the form of poor physical condition, impaired function of the legs and the above-mentioned autonomic neuropathy, which itself causes changes in the pulse (710). The result is considered to be positive if the patient gets chest pains and special changes can be detected in the electrocardiogram during stress and/or the patient’s blood pressure falls. Certain changes in the resting electrocardiogram (blood pressure changes, atrial fibrillation, heart block) and treatment with certain types of drug render interpretation of the results difficult. The test will therefore often be worthless. Signs of ischaemia in the electrocardiogram without accompanying chest pain during stress testing with ECG are always seen in Type 2 diabetes patients with heart disease, but are unfortunately often also seen in patients without. Thus only approximately half of patients with asymptomatic myocardial ischaemia will have treatment-requiring narrowing of the coronary arteries (711). Concomitant occurrence of albuminuria increases this percentage (711). In contrast, however, if chest pains occur during the test (i.e. a positive test), the value of the stress test with ECG is similar to that in patients without diabetes, and it is natural to thereafter examine the patient by CAG. If the test is negative, the risk of cardiovascular disease depends on the risk factors. The value of the test in general screening of Type 2 diabetes patients without heart symptoms is thus unknown.

Investigation of the heart with isotopes (myocardial scintigraphy). If the stress test with ECG cannot confirm or disprove suspected heart disease, and especially if the electrocardiogram exhibits signs of asymptomatic myocardial ischaemia, many centres will perform myocardial scintigraphy (712). By concomitantly stressing the heart muscle pharmacologically to imitate physical work, or by administering vasodilators, myocardial scintigraphy can be used to determine whether the coronary arteries are significantly narrowed. With a positive test one will proceed with CAG, while a negative test indicates a low risk of heart disease, also in diabetes (710). In the case of silent myocardial ischaemia during stress testing with ECG, some doctors prefer to proceed directly to CAG due to the high probability of finding treatment-requiring stenoses (50%) (711). These various procedures have not been compared scientifically, however. The value of myocardial scintigraphy as a screening method is unknown.

Ultrasound examination of the heart under stress (stress echocardiography). Ultrasound investigation of the heart – echocardiography – is presently used routinely to estimate the heart’s overall pumping ability and to identify areas with permanently impaired contractility reflecting a previous cardiac infarct. Echocardiography under physical strain/stress – stress echocardiography – can detect localised impaired contractility and hence locally impaired blood supply to an area of the heart due to a narrowed coronary artery. The examination requires considerable expertise and is therefore only performed at few centres in Denmark. Only a single study of diabetes patients exists indicating that stress echocardiography can supplement stress testing with ECG to help identify patients at high risk (713).

Coronary arteriosclerosis by CT scanning and magnetic resonance (MR) imaging of the coronary arteries. The former method can quantify and locate the calcium deposits in the coronary arteries. Only a few studies of Type 2 diabetes patients exist, and the value of the test for diagnosing and determining the risk of heart attacks is presently unknown. MR scanning of the coronary arteries could become an important examination in the future as a possible substitute for CAG.

Cerebrovascular atherosclerosis in Type 2 diabetes
As in patients without diabetes, cerebrovascular atherosclerosis provoke transient cerebral ischaemia (TCI) and cerebral infarcts in patients with Type 2 diabetes. Cerebral infarcts are seen earlier and more frequently in diabetes, and the mortality is greater. As is evident from Chapter 5, there is evidence that cerebral infarcts
can be prevented through intensive pharmacological treatment with acetylsalicylic acid, anti-hypertensive drugs and lipid-lowering drugs. Moreover, good glucose regulation entails a lower incidence of cerebral infarcts.

- **Ultrasound investigation of the cervical arteries: plaques and intima-media thickness (IMT):** Through ultrasound examination of the cervical arteries it is possible to detect stenoses where emboli can form and travel to the brain. It is presumed that small emboli cause TCI, and that larger emboli cause most cerebral infarcts (the remainder being caused by cerebral haemorrhage). The presence and type of plaque are associated with an enhanced risk of cerebral infarct. It is only advantageous to administer anticoagulation drugs and to surgically rectify the stenosis in cases where the latter is pronounced. In other cases the approach is intensive treatment of the risk factors. In large population studies the thickness of the two innermost layers of the arterial wall, the intima and media – the intima-media thickness (IMT) – has been found to relate to an enhanced risk of both myocardial infarcts and cerebral infarcts (714). In diabetes this relation is less pronounced, among other reasons because diabetes per se enhances the IMT (715). The value of screening for cardiovascular disease with ultrasound of the cervical arteries is unknown, and the significance of IMT as a risk factor is uncertain in Type 2 diabetes.

**Atherosclerosis in the leg vessels in Type 2 diabetes**

Impaired blood flow in the legs can cause pain or weakness of the calves during walk (claudicatio) and in the worst cases cause foot ulceration and gangrene leading to amputation.

Before ulcers and the risk of gangrene arise, examination of the feet will show signs of impaired blood supply in the form of thin, shiny skin, discoloration and not least the lack of a pulse in the foot. Impaired blood flow in the legs is accompanied by a great risk of not only gangrene, but also of cerebral and myocardial infarction. The Working Group is therefore of the opinion that these patients should be intensively treated for possible risk factors (Chapter 5), even though the evidence for this is not as good as for the heart patient.

The value of clinical examination of the feet as part of a screening programme has been discussed above (Section 6.2.4). As far as concerns blood flow, the main element of such a programme – test for a foot pulse – is subject to uncertainty, however, with many false negative and false positive results (716). Moreover, it would be appropriate if progressive atherosclerosis could be detected earlier.

- **Angiography of the leg vessels.** This can be performed either by introducing a catheter into the bloodstream and injecting contrast medium (invasive) or by means of magnetic resonance angiography. The former method is risky, and both are expensive. Even though both can diagnose stenosis of the arteries, as with the coronary angiography, it is not realistic to screen large groups of patients devoid of symptoms of atherosclerosis.

- **Measurement of blood pressure in the leg and the ankle/arm index.** The ratio between the blood pressure in the ankle and in the upper arm falls with decreasing blood flow in the legs. Among patients without diabetes, the ankle/arm index is very likely to identify patients with treatment-requiring stenosis of the leg arteries (index <0.9). If the index is normal, the arteries are very likely to be normal (716). In diabetes, measurement of the blood pressure in the ankle is subject to great uncertainty due to stiffness of the vessels for reasons other than atherosclerosis. The number of false negative results is therefore too great for the test to be useful for screening. An ankle/arm index under 0.9 in diabetes is always an expression of a serious impairment of the blood supply. Like the ankle/arm index, the increased stiffness of the vessels is a risk factor for cardiovascular mortality (717), but whether measurement of the stiffness of the vessels can be used to screen for subclinical atherosclerosis in the legs is as yet unknown.

**Subconclusion**

- There is no risk-free, commonly available and reliable screening test that with reasonable certainty can diagnose progressive atherosclerosis before the appearance of symptoms or clinical signs of disease.

- Upon symptoms or signs of heart disease, Type 2 diabetes patients should be examined for coronary atherosclerosis with the available methods and in the same manner as persons without diabetes (1c).

- The same should be considered if the patient is highly at risk due to accumulated risk factors, albuminuria, the presence of atherosclerosis elsewhere or signs of asymptomatic myocardial ischaemia in the electrocardiogram. The utility of this should be investigated scientifically (2b).
6.3 The patient

The general aspects regarding the patient’s expectations and reaction to screening have been addressed in Chapter 3. With screening for late complications in particular, it has been shown that knowledge and understanding of the disease is essential if the patient is to be able to manage the practical aspects of prevention, control and treatment of late complications (718) (3b) (719) (3b) (720) (3b). Moreover, knowledge and understanding are a precondition for avoiding the anxiety and depression that can otherwise occur in patients who fear the risk of development of late complications, especially blindness (721) (3b) (722) (3b). Finally, knowledge and understanding are motivation factors for attending recommended out patient check-ups. Regulation of diabetes has been shown to be significantly better in patients who attend regular check-ups than in patients who do not (723) (3b).

Diabetes patients themselves are very interested in receiving diabetes education (724) (3b), but optimal education requires engagement and attendance by the patient (725) (3b) (719) (3b) (723) (3b). This will be stimulated if the patients meet healthcare practitioners who are considered to have good human characteristics and a high professional level (718) (3b) (719). On the other hand, patients who benefit from the education are better able to follow the recommended lifestyle rules and to optimise their blood glucose regulation (726) (3b) and among other things require fewer and shorter diabetes-related hospital admissions (727) (3b) (728) (3b).

The key concept in the healthcare system’s attitude to diabetes patients is “help to be able to provide self-care”. It is thus important that lifestyle advice and guidance does not attain the character of cooperation agreements, but rather of partnership agreements where the diabetes patient’s own experiences are incorporated (729) (3b) (730) (3b). This optimises the possibility that the choices the diabetes patients make regarding their own life situation will be personally meaningful and help prevent and alleviate the negative consequences of the diabetes on the course of their lives (731) (3b) (732) (3b).

Subconclusion

- The patient’s own knowledge and understanding of prevention, control and treatment of late diabetic complications play an important role in limiting their occurrence and progression (3b).

6.4 Organisation

Retinopathy

Effective screening for diabetic retinopathy in Type 2 diabetes requires that the patients are offered and participate in screening. This is by far the case, however. A study from Vejle County showed that only 46% of Type 2 diabetes patients had been examined at an ophthalmologist during the course of 1997, while 26% had not been examined during the period 1993-1997 (521) (1b). The reason for this discrepancy had not been clarified in detail, but is probably due to a number of factors, for example that the patients had not been made aware that they should see an ophthalmologist, poor patient compliance and variation in the accessibility of the ophthalmology services.

Screening for diabetic retinopathy can be undertaken by persons with various degrees of ophthalmologic education:

- Ophthalmologists specializing in diabetic retinopathy
- Non-specialised ophthalmologists or technicians trained in ophthalmology
- General practitioners.

There is a clear correlation between the quality of the screening and the educational status of the screener (733) (1a) (734) (1a). Thus one study showed that the quality of screening for retinopathy in Type 2 diabetes patients performed by general practitioners was significantly lower than the optimal standards for ophthalmoscopy/fundus photography, with a sensitivity of 62.6%/79.2%. The specificity for detection of early changes was 75.0%/73.5%, while that for detection of sight-threatening changes was 93.8%/84.8% (655) (2b). Another study showed that identification of early or sight-threatening changes could be carried out by general practitioners with a sensitivity of 52% and a specificity of 84% compared to non-specialised ophthalmologists (2b), while a third study showed that the demonstration of early or sight-threatening changes can be undertaken by general practitioners with a sensitivity of 41% to 67% and a specificity of 86% to 94% compared with a technician trained...
in ophthalmology (2b). Even trained ophthalmologists risk overlooking up to 50% of the very earliest changes with ophthalmoscopy and consequently of making a wrong recommendation regarding the interval to the next check-up (660) (2b). It can be expected that telescreening, whereby fundus photography is undertaken de-centrally and sent for gradation at a centrally located specialist via the Internet, could one day become an alternative organisational solution to screening for diabetic retinopathy (664) (1b). This organisational principle can be an alternative in cases of a shortage of ophthalmologists or in areas where the distance to an ophthalmologist is great; moreover, it provides the possibility for central registration of screening activities with a view to systematic quality assurance (512) (1a) (594) (1a).

Nephropathy/hypertension and neuropathy
There are no systematic studies of different ways of organising screening for diabetic nephropathy/hypertension and neuropathy. However, studies indicate that central registration of diabetes patients better enables systematisation, standardisation and quality-assurance of check-up and treatment of the late diabetic complications, as well as the possibility to provide examinations to patients who fall outside the routine surveillance system (512) (1a) (594) (1a).

Feet
In principle, screening can be undertaken by a specially trained nurse, a physician or podiatrist, either in general practice or as part of a centralised diabetes team. The RCTs available concern screening by experienced staff at centralised hospital units. Other studies, however, indicate that good results can be obtained in general practice. As diagnosis and treatment of foot ulcers and infection are difficult, this aspect should be centralised in multidisciplinary treatment teams consisting of a diabetologist, specialised nurse, podiatrist, orthopaedic/vascular surgeon and an orthopaedic shoemaker/surgical appliance maker.

Cardiovascular disease
Electrocardiography and measurement of blood pressure, lipids and albumin/creatinine ratio in spot urine can be undertaken in the primary sector or at a hospital diabetes clinic (512) (1a). Extended cardiological examination requires referral to cardiology outpatient clinic.

Subconclusion
- If screening for late complications in Type 2 diabetes is to be effective, it has to be made available to everyone.
- Screening for late diabetic complications can be carried out in the primary sector or in the secondary sector.
- The degree of specialisation of the person carrying out the screening examination is decisive for the quality of the examination. This can speak in favour of centralisation and team formation with respect to certain types of screening activities, for example diabetic foot problems and gradation of diabetic retinopathy (1a).
- Even for experienced retinal specialists, screening using an ophthalmoscope will, in contrast to fundus photography, entail a more than 50% risk of overlooking the earliest changes, with the consequent risk of incorrect recommendation about the optimal check-up interval (2b).
- Telescreening for diabetic retinopathy can combine the need to enhance decentral accessibility to the examinations with the need to perform specialised gradation centrally. This can be an alternative in cases where there is a shortage of ophthalmologists or in areas where the distance to an ophthalmologist is great (1b).
- Central registration of patients with Type 2 diabetes better enables systematisation, standardisation and quality-assurance of control and treatment of the late diabetic complications, and provides the possibility to provide examinations to patients not encompassed by the routine surveillance system (1a).

6.5 Economy

6.5.1 Retinopathy
The aim of the cost-effectiveness analysis is to assess the cost-effectiveness of screening for diabetic retinopathy among patients with diagnosed Type 2 diabetes. The analysis comprises three different levels of screening and an alternative without systematic screening: Level 1 (screening by hospital), level 2 (screening by ophthalmologist), level 3 (screening by general practitioner or optician) and level 4 (no systematic screening). The four alternatives are illustrated in the decision tree shown in Figure 6.5.1, where the outcome targets are years without sight and quality-adjusted life-years, respectively.
A Markov model has been used to model costs and consequences of screening versus no screening for a cohort of patients over a period of time. The model has been adapted to a version of a model elaborated by Drs. M. James and R. Little from the Centre for Health Planning and Management, University of Keele in connection with a corresponding project at the UK National Institute for Clinical Excellence (NICE). As organisation of screening for retinopathy in England does not follow that in Denmark, and as the costs differ, parts of the model have been reprogrammed. Moreover, as clinical literature studies in Denmark have revealed different outcome data, a sensitivity analysis has been carried out for the two studies. The Danish model uses transitional probabilities calculated on the basis of data from the Wisconsin study and recent European figures calculated by professor Toke Bek for the determination of transitional probabilities, while the English data are based solely on the Wisconsin study.

Annex 9a shows a schematic overview of the overall structure of the model. The first part of the model shows the number of Type 2 diabetes patients and sets the number of registered and non-registered patients, respectively. Patients who are not registered proceed to that part of the model where no screening is undertaken (Annex 9b), while the registered patients are offered screening. Those patients who reject the programme proceed through the model without screening, while the remainder proceed to screening (Annex 9c). The model’s no screening alternative is in practice simplified as a number of patients who are not screened systematically might in practice contact the healthcare system if they have problems with their sight and be offered treatment for retinopathy in cases where this is diagnosed. Thus the model will probably underestimate the costs and effects of the alternative without screening. As no data exist concerning patients who contact the system themselves, this alternative has not been examined further.

The probability of going from one state to another in the model depends on the subgroup to which the person belongs. Initially, no one in the cohort has retinopathy. During the course of time, part of the cohort will go from no retinopathy to early retinopathy, to sight-threatening retinopathy and finally to blindness. Moreover, in all states there is a risk of mortality – depending on age and type of diabetes.

In those parts of the model in which screening is undertaken (Annex 9c), the patient passes through the same health states as in the model without screening (Annex 9a). The screening identifies patients with sight-threatening retinopathy. These patients are presumed to undergo laser treatment and are subsequently gathered in the group for avoided sight-threatening retinopathy. As the literature provides no evidence for how long the patients benefit from the treatment, the effect is presumed to last for the rest of their lives. However, annual screening is performed in order to monitor the condition of the patients, thus entailing a cost without any further increased health benefit. For the group of patients where sight-threatening retinopathy is avoided, the same transitional probabilities are used as in the model without screening. The transitional probabilities are shown in Annex 10.

In that part of the model where screening is performed the cohort is subdivided into patients with positive and negative tests, respectively (Annex 9b). The group with a negative test consists of persons without sight-threatening retinopathy (the true negatives) and persons who are incorrectly identified as not having sight-threatening retinopathy (the false negatives). The persons with negative tests are not offered treatment, and the course of their disease will be unaffected by the screening, while patients with false positive tests are assumed to be correctly identified after one referral to a hospital, which entails an extra cost over and above the screening itself. The persons with sight-threatening retinopathy are offered laser treatment, and it is assumed that all patients in the group will accept this offer. If the treatment is successful, the patients are transferred to the group with avoided sight-threatening retinopathy – if not, the person stays in the group with sight-threatening retinopathy.
The model is based on a cohort of persons similar to the Danish population. The number of persons with Type 2 diabetes has been set to 100,000 patients, who are assumed to be offered screening for retinopathy once per year. The patients who accept the screening and test positive will subsequently receive treatment.

In the model screening is initiated at age 57 years, corresponding to the median age for developing Type 2 diabetes, and runs up to the mean life expectancy in Denmark, which is approx. 78 years. The cohort thus undergoes 22 rounds of screening, with each round reducing the cohort by the sum of the probability of dying (which follows the general population) and the excess mortality entailed by Type 2 diabetes. These assumptions are a simplification of reality, but there are no studies available describing the prevalence of retinopathy in an unselected population of patients with Type 2 diabetes. Similarly, it has not been possible to model the possibility that elderly persons with newly diagnosed Type 2 diabetes could be screened less often. Due to the lack of data on prevalence and incidence of diabetes and retinopathy apportioned by age group the course modelled in practice is that of an average person with diabetes, who represents all persons in the cohort.

**Effectiveness of screening**

The sensitivity and specificity of the alternative organisational models are based on estimates made by Professor Tøke Bek. The estimates are founded on fundus photography and gradation by an experienced specialist at a centralised unit as the gold standard. Based on this, a specialist who performs the examination by ophthalmoscopy or who has no special experience in assessing fundus photographs will identify “no retinopathy” as “early retinopathy” in 67% of cases and “early retinopathy” as “sight-threatening retinopathy” in 90% of cases, but will always categorise “sight-threatening retinopathy” correctly. In practice, this means that all the organisational models correctly identify persons with sight-threatening retinopathy and hence save equally many sight-years, but that they differ as to how many patients will be categorised as false positive. The estimates used are essentially different from those used in the English model, among other reasons due to differences in organisation of screening in England and Denmark. Sensitivity analyses have been performed in order to evaluate the significance of these differences.

**Effectiveness**

The model uses foreign QALY values based on Drummond (1987) (735), Javitt (1996) (736) and Brown (2000) (737). One year in the state “no retinopathy” and “early retinopathy” is accorded 0.89 QALY, “sight-threatening retinopathy” before and after successful treatment is accorded 0.74 QALY, while “blind” is accorded 0.4 QALY. That no Danish values are used is obviously a weakness of the study. The model results are not sensitive to changes in how the values are weighted. Moreover, the number of years of blindness is used as the outcome measure.

**Costs**

The costs of screening and treatment have been determined by questioning a reference group of clinical experts consisting of Professor Tøke Bek, Ophthalmology Department, Aarhus University Hospital, Professor Nicolai Larsen, Steno Diabetes Center and ophthalmologist Svend Krag, Holstebro.

The costs of the three alternatives are:

**Level 1. Screening by the hospital**

- Nurse, approx. 5/6 hour at approx. DKK 180=DKK 150
- Ophthalmologist, approx. 1/12 hour at approx. DKK 330=DKK 28
- Film, eye drops, cotton wool, etc.=DKK 25

On top of this comes the expense for a fundus camera, which costs approx. DKK 300,000 to buy and is depreciated over 5-10 years. It is assumed that the camera is used 2,000 times per year for five years, and that it needs annual maintenance valued at 10% of the original cost price such that the equipment costs amount to DKK 48 per screening examination. The total costs per examination that can be directly ascribed to the patient thus amount to DKK 251. Assuming as a rule of thumb that half of the costs at the outpatient clinics can be ascribed to the patient, each examination actually costs DKK 502, fully inclusive. This sum can be compared with the DRG rate for a casualty ward visit (DKK 580), which from the point of view of consumption of time and resources is reasonably comparable with screening for retinopathy.
Level 2. Screening by ophthalmologist
Examination by an ophthalmologist entails payment of a fixed fee by the Health Insurance of DKK 183.96 for the initial consultation and DKK 81.96 for the subsequent consultations. Consultations held more than six months after the preceding consultation are considered to be initial consultations.

A special examination for diabetes entails an additional fee of DKK 176.59. A diabetes check-up by an ophthalmologist thus costs DKK 360.55 per year.

Level 3. Screening by general practitioner or optician
There is no experience with this alternative in Denmark, and the model therefore uses DKK 300 as a reasonable estimate. Unfortunately it has not been possible to specify the costs more accurately and the cost is therefore only relevant as the basis for a sensitivity analysis.

If sight-threatening changes are identified
If sight-threatening changes are identified through screening the patient is referred to an ophthalmology department for specialist examination. The examination involves 30 minutes of ophthalmologist time, 30 minutes of nurse time and expenses of approx. DKK 20 for the use of consumables – a total of DKK 275 that can be directly ascribed to the individual patient.

In an estimated 10% of cases, fluorescence angiography is undertaken. This entails the one hour of angiography nurse time, consumables for DKK 170, 12 minutes of secretary time at DKK 120/hour and 30 minutes of ophthalmologist time. On top of this comes DKK 64 per examination for depreciation and maintenance of equipment – a total of DKK 614 per examination.

The first examination after the identification of sight-threatening retinopathy thus amounts to an average of DKK 309. If overhead is added, the cost is DKK 618.

If laser treatment is to be undertaken, this entails expenses for 30 minutes of ophthalmologist time and for 30 minutes of nurse time. The laser costs DKK 500,000 and is depreciated over 5-10 years. If the laser is assumed to be depreciated over 5 years and is used 700 times per year, the costs amount to DKK 229 per treatment. Laser treatment is performed an average of 3.5 times on each eye in the case of proliferative diabetic retinopathy and once per year in the case of diabetic maculopathy. As these disorders occur in half the cases, 2.25 laser treatments are performed on average. An average course of laser treatment thus costs DKK 1,089 – or DKK 2,178 inclusive overheads.

In some cases, vitrectomy is undertaken. Aarhus County charges DKK 30,000 for this procedure, inclusive hospital admission, which is the estimate used in the model. It is assumed that vitrectomy is undertaken in 20% of the cases in which sight-threatening changes are found.

In cases of sight-threatening changes a course of treatment costs an average of DKK 8,175. If the examination costs are added, the total amount is DKK 8,793.

Discounting
A discounting rate of 5% is used for both expenses and effect, and sensitivity analyses have been undertaken for 0.3% and 6%, respectively, although this has not influenced the conclusions.

Fixed costs
The establishment of systematic screening requires a register of all patients with Type 2 diabetes such that the patients can be summoned in a coordinated and planned manner. This applies whatever the choice of organisational model. The register is also necessary if another form of screening is to be initiated. The cost of operating such a register is estimated at DKK 1 million per year. The results are not sensitive to this estimate. It is assumed that 90% of patients with Type 2 diabetes will be registered and that 90% of the registered patients will accept the offer of screening. Furthermore, it is assumed that those patients who do not participate in the screening will never accept the offer of screening. The model’s conclusions are not sensitive to changes in the stated parameters as the fixed costs of the screening programme are relatively small.

Costs associated with blindness
The costs of blindness can be subdivided into five categories: 1) costs for support and care, 2) costs for aids, 3) costs for education, 4) other direct costs and 5) production loss for society.
Support and care:
The costs for support and care primarily encompass an escort scheme and domestic assistance. By law, a blind person has the right to 180 hours of escort help per year, which virtually all blind persons are estimated to use. According to Næstved Municipality and a user-helper contact bureau “Bruger-Hjælper Formidlingen”, it costs approx. DKK 200 per contact hour to supply this service. Valdemarsgade Handicap Centre states that a newly blind person receives two additional hours of domestic assistance per week compared with a sighted person having the same profile. The price per contact hour is stated to be approx. DKK 200. The total annual costs for support and care thereby amount to DKK 56,800.

Aids:
Blind and partially sighted persons receive a number of aids from the County, the Municipality and the State. By far the majority of blind people receive aids such as walking sticks, tape-recorders and note-taking appliances. The Danish Association of the Blind states that the provision of aids of this type costs approx. DKK 2,500 per year. A small but increasing proportion of blind people receive various IT aids. A complete IT solution for a blind person costs approx. DKK 100,000, while a smaller IT solution consisting of a PC and compensatory speaking equipment costs approx. DKK 30,000. Assuming that the IT equipment is depreciated over 5 years the annual cost will be somewhere between DKK 6,000 and 20,000. The number of blind people provided with an IT solution is unknown, however. Partially sighted people often receive a number of optical solutions costing approx. DKK 15-20,000.

Guide dogs are only used by the minority of the blind people, but on the other hand are relatively expensive. A guide dog costs DKK 160,000 and is in active service for approx. 10 years. There are 219 trained guide dogs in Denmark. Assuming that the dogs primarily go to persons among the 5,000 blind people (in contrast to the partially sighted persons) the average annual guide dog costs per blind person are approx. DKK 700.

The Danish National Library for the Blind converts written sources to spoken word and lends materials to the blind and partially sighted. In 2000 the marginal costs, i.e. excluding costs for the manufacture of the materials etc. amounted to an average of DKK 4,122 per borrower, inclusive expenses for postage paid by Post Denmark. Approximately 10,000 blind and partially sighted persons are registered borrowers at the Danish National Library for the Blind.

In addition to this, the Municipalities provide a number of aids, such as speaking balances and clocks, special lights for the partially sighted etc. However, there is no overview over how great a proportion of blind people have such aids, which makes it difficult to calculate the associated total annual costs. Based on the available information this has been estimated at approx. DKK 10,000 per year.

Education:
The Institute for the Blind and Partially Sighted arranges individual courses for the blind and partially sighted. The courses cost between DKK 147,000 and 293,000. It is unclear how great a proportion of the persons who have become blind due to Type 2 diabetes participate in these courses. In addition, the institute holds senior courses for blind and partially sighted citizens of Copenhagen. These courses cost approx. DKK 40,000. No comparable alternative exists in the remainder of the country.

Other services:
Over and above the costs already mentioned there are a number of costs that are difficult to calculate and to ascribe to the individual patient, and hence are omitted from the analysis. Among others the omitted costs include expenses for:

- The Danish Association of the Blind
- The blind consultancy scheme
- Vision consultancy scheme
- Knowledge Centre for Visual Disability
- KLO – (Culture and Literature Orientation for Visually Handicapped People)
- Municipal spoken newspapers
- Copenhagen Municipal Library Sound Production
- Various municipal library initiatives with workplaces for the blind
- Purchase of recorded books
- Informal help from relatives
- Various transport expenses.
Production loss
More than 85% of blind people in the age group 51-60 years receive a state disability pension, and less than 10% are actively employed under normal employment conditions (738). For by far the majority the loss of sight means that they are no longer active on the labour market. However, as patients with Type 2 diabetes often do not lose their sight until a relatively high age, the production loss for society will be limited. Moreover, as there are a number of ethical problems associated with the inclusion of costs related to production loss, the latter have been omitted from the analysis. The sensitivity analyses undertaken show that this decision does not affect the results of the model calculations.

Total annual costs associated with being blind
As is apparent from the above review, it is difficult to obtain an exact picture of the annual costs entailed to society by a person becoming blind. Based on escort schemes, domestic assistance and aids, the total costs are estimated to be approx. DKK 70,000 per year, which is the cost estimate used in the model. The real total costs are probably higher.

Results of the model calculations
Table 6.5.1 shows the modelled costs and consequences in present monetary terms of the four alternatives for the cohort of persons with Type 2 diabetes over the 22-year period covered by the model. As is apparent, the effect of the screening alternatives is identical as all models identify sight-threatening retinopathy correctly, and as treatment is only initiated if sight-threatening retinopathy is present. The lowest level of screening (level 3) incorrectly identifies a number of the early cases of retinopathy as sight-threatening retinopathy, and hence will entail costs for further examination.

With reservations for the simplifications and limitations encompassed by the model analyses, screening and treatment of retinopathy are appropriate uses of resources as the total costs for the screening models are considerably lower than for the model without screening in that costs saved by the reduction in the number of persons becoming blind considerably exceed the costs of intervention. Given the assumptions made there is no difference in the sensitivity of the various models for screening for retinopathy of any consequence for the transition to the blind state. The organisation of screening should therefore be determined from the cost of the different alternatives. Screening at hospitals is the cheapest alternative if the estimated overhead expenses are excluded, but the most expensive if they are included. Unfortunately it has not been possible to perform more detailed analyses of the costs of screening with the various organisation forms, and a decision on to how screening should be organised should therefore be based on concrete costs from the different organisation forms.

**TABLE 6.5.1**

<table>
<thead>
<tr>
<th>Screening incl. fixed costs</th>
<th>False positive</th>
<th>Examination/ treatment of false positives</th>
<th>Total health costs</th>
<th>Costs entailed by blindness</th>
<th>Total costs</th>
<th>Total QALY</th>
<th>No. of saved sight years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>535,896</td>
<td>109,564</td>
<td>468,302</td>
<td>983,851</td>
<td>1,641,953</td>
<td>940,329</td>
<td>76,137</td>
</tr>
<tr>
<td>Level 2</td>
<td>344,066</td>
<td>109,564</td>
<td>468,302</td>
<td>983,851</td>
<td>1,420,743</td>
<td>940,329</td>
<td>76,137</td>
</tr>
<tr>
<td>Level 3</td>
<td>261,838</td>
<td>9,147</td>
<td>109,564</td>
<td>983,851</td>
<td>1,377,043</td>
<td>940,329</td>
<td>76,137</td>
</tr>
<tr>
<td>No screening</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4,312,324</td>
<td>4,312,324</td>
<td>925,113</td>
</tr>
</tbody>
</table>

In order to estimate the annual costs and effects for one year for a population similar to the Danish population the age profile and the retinopathy profile of 100,000 persons with Type 2 diabetes have been modelled on the basis of assumptions about mortality and the course of the disease. This estimate is shown in Table 6.5.2.

**TABLE 6.5.2**

<table>
<thead>
<tr>
<th>Screening incl. fixed costs</th>
<th>False positive</th>
<th>Examination/ treatment of false positives</th>
<th>Total health costs</th>
<th>Costs entailed by blindness</th>
<th>Total costs</th>
<th>Total QALY</th>
<th>No. of saved sight years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>45,496,280</td>
<td>6,506,398</td>
<td>53,204,678</td>
<td>58,379,484</td>
<td>110,724,163</td>
<td>86,575</td>
<td>4,529</td>
</tr>
<tr>
<td>Level 2</td>
<td>32,538,705</td>
<td>6,506,398</td>
<td>39,544,094</td>
<td>58,379,484</td>
<td>97,564,388</td>
<td>86,575</td>
<td>4,529</td>
</tr>
<tr>
<td>Level 3</td>
<td>29,395,319</td>
<td>54,100</td>
<td>36,445,638</td>
<td>58,379,484</td>
<td>94,965,102</td>
<td>86,575</td>
<td>4,529</td>
</tr>
<tr>
<td>No screening</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>256,497,062</td>
<td>256,497,062</td>
<td>84,758</td>
</tr>
</tbody>
</table>

Type 2 diabetes. Health Technology Assessment of screening, diagnosis and treatment
Sensitivity analysis
A number of sensitivity analyses have been performed. Apart from the cost of the screening itself and the ability of the models to correctly identify patients with sight-threatening retinopathy, the results generated by the models are not sensitive to changes in the underlying parameters. The results of a sensitivity analysis made using English-inspired data for sensitivity and specificity are shown in Annex 11. From this it can be seen that even with a relatively small misjudgement of when the patient has sight-threatening retinopathy, the savings associated with screening at a lower level will relatively rapidly be counterbalanced by the increased costs of blindness. Given the assumption made in Annex 11, screening at level 2 will be cheapest, while the costs per QALY of going from the middle level to the highest level will be approx. DKK 80,000.

Health economic subconclusions as regards screening for diabetic retinopathy
- The figures calculated with the model show that systematic screening for retinopathy will entail a net saving for society while concomitantly improving the patients’ quality of life. Such calculations are based on a large series of assumptions, but the sensitivity analyses have not changed the overall conclusions.
- Health economic considerations indicate that systematic screening for retinopathy should be implemented, but that the strengths and weaknesses of the alternative screening models should be analysed more closely than has been possible in this study. In particular, the ability of the models to correctly identify patients with sight-threatening retinopathy and the costs of the alternative screening models should be examined more closely.
- Compared with the situation without screening, the introduction of systematic screening of the Type 2 diabetes population for retinopathy will entail annual health costs of up to DKK 52 million.
- As screening for retinopathy is already being carried out in many parts of the country, the annual cost of general screening will not entail health costs of up to DKK 52 million specified in Table 6.5.2.
- No figures are available in Denmark to indicate how many people are already being screened at present and at what level. Thus it is not possible to estimate the health costs of extending the screening to everyone with Type 2 diabetes. Correspondingly, general screening will not entail the above-mentioned health benefits either since part of such benefits can already be expected to have been attained.

6.5.2 Nephropathy/hypertension
In the technology section, no studies, were identified which could identify any actual relationship between screening for nephropathy/hypertension in patients with Type 2 diabetes and effects on the final health-related outcomes such as mortality and avoided dialysis treatment. Thus it has not been possible to perform an actual health economic analysis that relates the costs to the effects of intervention. Even though no studies were identified that directly documented the relationship between screening and the health-related outcomes, this does not mean that early treatment does not work. There is general agreement that screening for nephropathy and hypertension is beneficial to the patients, just as it is documented that early treatment prevents progression of the diabetic nephropathy. It is difficult to precisely estimate the magnitude of the effect of screening per se, however.

If the screening is organised at the general practitioners and entails measurement of blood pressure and urine albumin, the cost based on the current fees will be DKK 92.55 per patient (DKK 83 for the consultation and DKK 9.55 for urine analysis with test strip) (739). If the urine analysis is negative, microalbuminuria is tested for annually. This is done by sending a sample to a laboratory, which costs DKK 61.55 per patient (source: Copenhagen General Practitioners’ Laboratory). It is not known what proportion of the urine analyses are negative, and it is not known how often microalbuminuria is tested for. Assuming that 100,000 patients will have to have their blood pressure measured and their urine examined for protein once per year, the total annual costs for screening will be DKK 9.26 million. On top of this comes the annual costs for analysis for microalbuminuria and the costs for a diabetes register and subsequent treatment, etc. The diabetes register costs will cover other purposes than just screening for nephropathy, however.

A primary reason for screening for nephropathy is to avoid the necessity for dialysis. However, as the magnitude of the risk reduction with screening is unknown, it is difficult to estimate the saved dialysis costs. The annual costs for dialysis treatment per patient are approx. DKK 300,000 (740). If a screening campaign can reduce the number of years in dialysis by approx. 50, it will in itself justify the expenses for the annual screening. Based on expert opinion it is estimated that screening can reduce the number of patients needing dialysis by approx. 25%, and as it is estimated that 4.8% of patients with Type 2 diabetes will need dialysis, a 25% reduction will have a very great health economic potential that clearly exceeds the costs of the screening. Due to the lack of studies on this aspect, however, the evidence is considered to be too uncertain to allow actual health economic calculations to be made.
6.5.3 Neuropathy

Independent health economic calculations are not performed of screening for neuropathy as this is primarily aimed at preventing foot ulcers and thus overlaps screening for foot ulcers. Apart from foot ulcers, neuropathy is also associated with impotence etc., but there is no effective way of treating impotence. The technology section does not recommend independent screening for neuropathies other than peripheral polyneuropathy.

6.5.4 Screening for diabetic foot problems

The literature contains only very few studies of systematic screening for foot problems in patients with diabetes Type 2. It has only been possible to identify one randomised study that includes the economic aspects. The study was performed during the period 1989-1993 by McCabe et al. (493) and encompassed 2,001 patients associated with a diabetes outpatient clinic who were randomised to either a systematic screening and treatment programme or to the treatment normally provided by the system. Screening of 1,001 patients who were randomised to the intervention group identified 127 high-risk patients of whom 110 had previously been treated for foot ulcers or had deformed feet at the time of screening. These patients could – independently of the screening – have been identified earlier. The further 17 patients identified via the screening suffered from venous insufficiency. The study showed that screening and subsequent treatment reduced the number of major amputations significantly (1 in the intervention group versus 12 in the control group), while it was not possible to demonstrate any significant difference in the number of minor amputations. On the costs side, it was concluded that the saved costs for amputations almost counterbalanced the costs of the programme, thus rendering the programme cost-effective. The amputation costs were set very low, though, and expenses for rooms etc. in connection with the first screening were not included, and the analysis of the total costs should therefore be interpreted with caution.

The conclusions of the study are ambiguous. As far as high-risk patients are concerned there is little doubt that prevention and treatment are cost-effective. It is far more doubtful whether screening of low-risk patients is correspondingly cost-effective, however. The English study only identified 17 additional high-risk patients by screening – i.e. patients who would not already have been identified if a more effective register existed of patients who had previously been treated for foot ulcers. If the screening costs for the 1,001 patients are to be divided among the 17 patients, and it is assumed that one screening examination entails a visit to a podiatrist costing DKK 250, then the cost per additional high-risk patient identified will be approx. DKK 17,400. If this cost is ascribed to the patients in risk group 2 and 3, the costs per QALY will be DKK 250,000-300,000, cf. the model used in Chapter 4. This sum is somewhat above other public prevention strategies that are not generally offered at present, e.g. such as vaccination of elderly person.

Instead the efforts should be focused on high-risk patients, i.e. patients in risk groups 2, 3 and 4. In most cases these patients will already be or have been in contact with the healthcare system, and actual screening will therefore be unnecessary if an effective register can be established. The organisational feasibility of establishing administrative procedures to ensure that the patients are offered a prevention programme if risk factors are identified should therefore be determined since screening of all diabetes patients considerably raises the cost per identified high risk subject.

If it is not possible to establish administrative procedures to ensure that the patients are offered a prevention programme, general screening can be a possible alternative. In order to calculate the costs per identified high risk subject, knowledge is required about the annual incidence of developing the risk factors that characterise risk groups 2 and 3 in the model presented earlier in the present HTA. The McCabe study identified 127 high-risk patients per 1,001 screened persons, but as the screening was first-time screening, the figure is far higher than what can be expected upon annual routine screening as many of the patients in the risk group will have been identified at earlier screening rounds.

If it is nevertheless decided to undertake a screening programme for foot problems among all patients with Type 2 diabetes the total costs of the screening will depend on what agreements can be negotiated with the relevant organisation. Assuming that screening is to be undertaken by podiatrists once per year at a fee presently amounting to approx. DKK 250, the costs will amount to approx. DKK 25 million per year. To this should be added the cost of a register to ensure that the patients subsequently receive the correct prophylactic treatment. If the podiatrists are allowed to both screen and subsequently treat the patients, one has to be aware of the danger of supplier-driven demand, which will increase the costs of the programme. Finally, there are the costs for treatment of high-risk patients, but these costs will be counterbalanced by savings elsewhere in the system. One should be aware, though, that the costs and savings will not necessarily appear on the same budget within the system. The costs of screening could be reduced by prolonging the interval.
between the screening examinations, for example to three or five years. It is not presently possible to calculate the consequences of this because this requires knowledge about the incidence of the risk factors that can be identified by screening, knowledge of the proportion of the patients who would have found their way to the healthcare system independently of routine screening during the period in question, and information about the extent to which the effect of the prophylactic treatment is affected by it being initiated later in the course of disease – all of which is data that is not easily available at present.

From a health economic perspective there is no doubt that efforts should be made to establish organisational routines and an effective register to ensure that the risk patients who come into contact with the system will subsequently receive prophylactic treatment. If this is not possible, it is doubtful whether the alternative, i.e. annual general screening of all patients with Type 2 diabetes, comprises an appropriate use of society's resources, and knowledge is lacking about the consequences of screening at intervals of three or five years.

Health economic subconclusion regarding screening of diabetic foot problems

- It is recommended that guidelines and organisational routines should be drawn up and implemented to ensure that at-risk patients receive prophylactic treatment, and, secondarily:
- That Danish studies are carried out to document the costs and consequences of routine screening for foot problems in patients with Type 2 diabetes.

6.5.5 Diabetic cardiovascular disease

The literature search did not detect any reliable documentation that screening for cardiovascular disease in persons with Type 2 diabetes is beneficial. Thus it is not possible to undertake a proper health economic analysis.

In the technology section, stress testing with ECG, myocardial scintigraphy and stress echocardiography are emphasised as the presently most realistic screening possibilities for patients suspected of suffering from cardiovascular disease. If a screening programme should be initiated, the diabetes patients would initially undergo risk-assessment, and the at-risk patients would probably initially be offered stress testing with ECG. Such a stress test costs DKK 1,190 (source: Copenhagen General Practitioners’ Laboratory) over and above the costs associated with identifying persons at increased risk.

The problem with stress testing is partly that its specificity is relatively low, and partly that the ECG changes at rest and neuropathy in the patients often render the test inconclusive. In a relatively large proportion of the screened patients stress testing will therefore have to be supplemented with myocardial scintigraphy and/or stress echocardiography. Myocardial scintigraphy costs approx. DKK 4,500 (source: Rigshospitalet – Copenhagen University Hospital), and stress echocardiography costs DKK 4,155 (source: DKDRG-2003).

Final diagnosis is normally made by a coronary angiography (CAG) if the other examinations indicate that the person has cardiovascular disease. A CAG costs approx. DKK 12,000 (source: Gentofte Hospital and Rigshospitalet).

Over and above the screening costs there are the costs for examination and treatment of Type 2 diabetes patients with heart symptoms. It must be assumed, though, that these costs will be entailed irrespective of whether or not screening is performed as the patients will eventually develop such clear symptoms that examination and treatment will be initiated. There is no information available about how the later initiation of treatment affects treatment costs.

The exact number of patients who should undergo the recommended tests in not known. It is therefore difficult to provide a reasonable estimate of the annual costs associated with a screening programme for diabetic heart disease. The screening tests used are all relatively resource-demanding, though, and it must therefore be assumed that the total costs will also be relatively great. From a health economic perspective the resource consumption should always be related to the expected benefits. As long as our knowledge of the possible effect of screening and subsequent earlier intervention is so inadequate, systematic screening with the above-mentioned methods is hardly an appropriate use of society's resources. Studies should therefore be performed to clarify these matters before screening for diabetic heart disease is initiated.

Health economic subconclusion regarding screening for diabetic cardiovascular disease

No studies are available that can serve as the basis for an actual economic analysis of costs and benefits of screening for diabetic cardiovascular disease. However, as screening for diabetic cardiovascular disease will
entail considerable resource consumption and as the benefits must be assumed to be relatively limited, screening for diabetic cardiovascular disease will not comprise an appropriate use of society’s resources.

**Economic consequences of organisational aspects**

If a decision is made to screen for nephropathy/hypertension, diabetic cardiovascular disease and for the diabetic foot, the economically most appropriate approach would be to screen for all three conditions concomitantly. This would save consultation fees and will save time for the patient. As screening for nephropathy/hypertension and diabetic cardiovascular disease has to be carried out by a physician, in practice the general practitioner, screening for the diabetic foot would therefore also have to be carried out by the same physician in order to reap the benefits of combined screening. Screening for the diabetic foot entails testing peripheral sensation with a monofilament, pulse palpation and visual examination for foot deformities. An experienced physician would be able to perform the examination in about 10 minutes. Alternatively, the examination can be performed by a podiatrist, who can be expected to have greater expertise. No studies have been identified that compare the effect of screening examinations undertaken by different organisational levels.

Screening for diabetic retinopathy requires expertise as regards operation of the equipment and data analysis, which necessitates a certain degree of centralisation, for example at ophthalmologists. Moreover, the present development within information technology provides the possibility that examinations undertaken decentrally can be sent electronically to a central location for evaluation. This will combine the advantages of a widely available service for the patients with the possibility for centralised data analysis at a centre with great professional expertise. At the same time, this provides the possibility for systematic quality assurance of the screening activities.

All the fees and prices used are based on the existing organisation and the existing agreements between the organisations involved. If a decision is made to implement one or several of the screening models this will entail a very large number of services and it would therefore be appropriate to reorganise the services compared with their present organisation. The present organisation and fees should therefore be subject to closer analysis if it is decided to implement the recommended screening campaigns.

6.6 Overall conclusions and recommendations

**Retinopathy**
- Sight-threatening diabetic retinopathy can be identified by screening (1a), and can subsequently be treated by laser treatment, which reduces loss of sight by at least 50% (1a).
- Screening can be carried out by ophthalmoscopy or fundus photography (with documentation on photographic or digital media). The latter method is best suited for detecting the earliest changes (2b).
- The evidence suggests that screening for retinopathy should be carried out from the time Type 2 diabetes is diagnosed and the check-up interval thereafter adjusted to the severity of the retinopathy. Younger, poorly regulated patients should be screened annually. Elderly persons with newly arisen diabetes can be screened less frequently – as much as 4 years after the first examination if the result is normal (1b). A precondition, though, is that metabolic regulation remains acceptable.

**Nephropathy**
- Diabetic nephropathy is preceded by an asymptomatic period of albuminuria (1b).
- Diabetic nephropathy can potentially be prevented by early initiation of treatment with antihypertensive drugs (1b).
- Screening for albuminuria and hypertension should be carried out annually in the whole patient population (4).
- There are no studies clarifying the effect of screening *per se* on end-stage renal failure or on cardiovascular disease.

**Neuropathy**
- Approximately 8% of Type 2 diabetes patients have polyneuropathy in the form of loss of peripheral sensation or erectile dysfunction at the time the diagnosis is made, and approx. 25-40% after 10 years of the disease (1b).
- As all diabetes patients are at risk of developing neuropathy, the standard practice is to recommend screening of the whole diabetes population (4).
The diabetic foot
- The aim of screening for diabetic foot problems is to identify patients at risk of future ulceration and amputation. In such patients, education and treatment can reduce the frequency of amputation (1b).
- The diabetes patient’s foot problems encompass diabetic foot ulcers, amputations and abnormal posture.
- These problems are often preceded by a period of loss of sensation and increasingly impaired blood flow to the feet.
- The loss of sensation is most easily and precisely measured using a monofilament test (2b).
- It has been shown that monofilament testing has a high sensitivity and specificity for predicting subsequent foot problems (3b).
- There are no studies documenting how frequent the screening should be, but the general consensus is that it should be annual (4).
- Neither are there studies documenting which part of the health system should be responsible for the screening.

Cardiovascular disease
- There are no risk-free, commonly available and reliable screening tests that with reasonable certainty can diagnose progressive atherosclerosis before the appearance of symptoms or clinical signs of this disease (e.g., in the form of cardiac pain; angina pectoris).
- Upon symptoms or signs of heart disease, Type 2 diabetes patients should be examined for coronary atherosclerosis with the available methods and on the same basis as persons without diabetes (1c).
- The same should be considered if the patient is highly at risk due to accumulated risk factors, albuminuria, the presence of atherosclerosis elsewhere or signs of asymptomatic myocardial ischaemia in the electrocardiogram. The utility of this should be investigated scientifically (2b).

Organisation
- If screening for late complications in Type 2 diabetes is to be effective, it has to be made available to everyone.
- Screening for late diabetic complications can be carried out in the primary sector or in the secondary sector.
- The degree of specialisation of the person carrying out the screening examination is decisive for the quality of the examination. This can speak in favour of centralisation and team formation with respect to certain types of screening activities, for example diabetic foot problems and diabetic retinopathy (1a).
- Even for experienced retinal specialists, screening using an ophthalmoscope will, in contrast to fundus photography, entail a more than 50% risk of overlooking the earliest changes, with the consequent risk of incorrect recommendation about the optimal check-up interval (2b).
- Tele-screening for diabetic retinopathy can combine the need to enhance decentral accessibility to the examinations with the need to perform specialised gradation centrally. This can be an alternative in cases where there is a shortage of ophthalmologists or in areas where the distance to an ophthalmologist is great (1b).
- Central registration of patients with Type 2 diabetes better enables systematisation, standardisation and quality-assurance of control and treatment of the late diabetic complications, and provides the possibility to provide examinations to patients not encompassed by the routine surveillance system (1a).

Economic aspects
- Systematic screening for retinopathy will entail a net saving for society compared with the “imaginary” situation without screening, while concomitantly improving the patients’ quality of life. Such calculations are based on a large series of assumptions, but the sensitivity analyses have not changed the overall conclusions.
- Health economic considerations indicate that systematic screening for retinopathy should be implemented, but that the strengths and weaknesses of the alternative screening models should be analysed more closely than has been possible in this study.
- Compared with the situation without screening, the introduction of systematic screening of the Type 2 diabetes population for retinopathy will entail annual health costs of up to DKK 52 million.
- As screening for retinopathy is already being carried out in many parts of the country, the annual cost of general screening will not entail health costs of up to DKK 52 million.
- No figures are available in Denmark to indicate how many people are already being screened at present and at what level. Thus it is not possible to estimate the health costs of extending the screening to everyone with Type 2 diabetes. Correspondingly, general screening will not entail the above-mentioned health benefits either since part of such benefits can already be expected to have been attained.
The total cost of screening all Type 2 diabetes patients by measuring urine albumin and blood pressure is approx. DKK 10 million annually. As general screening for this is already being performed, the cost will not be the same as for the above-mentioned population screening, but will be less.

It must be expected, though, that such screening is particularly cost-saving since it can be expected to reduce the number of dialysis patients and dialysis costs approx. DKK 300,000 annually.

Guidelines and organisational routines concerning screening for diabetic foot problems must be drawn up and implemented to ensure that at-risk patients receive prophylactic treatment.

Likewise, Danish studies must be carried out to document the costs and consequences of routine screening for foot problems in patients with Type 2 diabetes.

**Recommendations**

- There is evidence that screening for diabetic retinopathy (and subsequent treatment) reduces the incidence of visual impairment and blindness (A), and that screening for diabetic foot problems with identification of patients with risk factors for diabetic foot ulceration and subsequent education and treatment of these patients prevent ulcers and amputations (B). In contrast, there is no evidence for isolated screening of other late diabetic complications.
- It is recommended that screening for diabetic retinopathy be performed by fundus photography (B).
- Screening for diabetic retinopathy should be performed in specialist clinics as the examination requires special apparatus (D).
- Telescreening for diabetic retinopathy via the Internet is a new organisational principle that can combine the need to enhance decentral availability of the examinations with centralised specialised gradation and registration for systematic quality assurance (A).
- Screening for diabetic foot problems could possibly be combined as a “package solution” with screening examinations for some of the late diabetic complications for which there is no evidence to suggest that they should be screened for in isolation, i.e. annual examination of the foot (sensation, pulse, skin and nails, and identification of any foot deformities) combined with measurement of albuminuria and electrocardiography. This screening is probably best undertaken by the Type 2 diabetes patient’s usual diabetes care practitioner (who should consequently be responsible for ensuring that it is carried out). As far as the feet are concerned, though, this is probably best carried out by a podiatrist (D).
- Due to the marked regional variation in the quality and extent of screening activity it is recommended that screening for late diabetic complications should be systematically registered in databases, and that its quality should be monitored (D).
7 Monitoring and quality assurance of treatment in Type 2 diabetes

Like other aspects of healthcare, diabetes treatment should be subjected to regular quality enhancement and assurance. As a basis for this, tools should be developed that at the national, regional and local levels in the individual department or individual general practice to ensure monitoring and optimisation of treatment quality through problem identification, establishment of quality targets, identification of relevant and manageable indicators for treatment quality, collection and analysis of data, quality improvement and monitoring.

The idea of quality assurance and monitoring of the quality of the diabetes treatment in Denmark is not new, for example having been put forward in the 1994 National Board of Health report on future organisation of diabetes treatment (1). At that time, the Working Group recommended monitoring based on systematic registration, collection and utilisation of data collected as part of the clinical routine in diabetes clinics and general practice. It was recommended that responsibility for registration should be assigned to the County diabetes committees, while overall responsibility for the elaboration of guidelines for monitoring should be assigned to the National Board of Health Diabetes Advisory Group.

Based partly on the above-mentioned recommendations the Danish Endocrinological Society started work on a national quality assurance database (DADIVOX), but the project was never realised. Corresponding initiatives in general practice (DiaDoc) and via the WHO (DiabCare) have never gained a foothold in Denmark. As a consequence, the existing quality assurance of diabetes treatment is sporadic, regionally based on locally developed databases and devoid of national coordination.

7.1 National and regional monitoring and quality assurance

To ensure future quality assurance of diabetes treatment in Denmark it is necessary to at minimum:

- Establish common national treatment goals
- Establish common national indicators for treatment quality
- Establish regional and national reporting and data analysis (clinical database)
- Establish a system for reporting to departments/general practice.

These national initiatives should be further supported by more comprehensive local monitoring, possibly adjusted to the specific conditions and the composition of the patient population in major diabetes clinics.

Common national treatment goals should be established based on the recommendations of the present HTA report. This task should be assigned to the National Board of Health Diabetes Advisory Group.

Common national indicators for treatment quality should be established in a narrow cooperation with the scientific societies and professional fora, but the number of indicators should be limited according to the recommendations of the National Competence Centre for Nationwide Clinical Quality Databases, Region East (http://www.kliniskedatabaser.dk).

Regional and national reporting and data analysis should take place to a national (or regional) clinical database. The clinical database should be established within the framework of one of the existing National Competence Centres for Nationwide Clinical Quality Databases (http://www.kliniskedatabaser.dk) according to the 2002 recommendations of the Danish Regions (the Association of Danish County Councils) (741).

Guidelines for reporting to departments/general practice should be established in cooperation with the scientific societies, other professional fora and the National Competence Centre for Nationwide Clinical Quality Databases.

The pre-existing clinical databases typically encompass a large or small number of treating hospital departments. With respect to the treatment of Type 2 diabetes, this mainly takes place in general practice. In order to ensure quality assurance in this area, registration should wherever possible be based on information already recorded in the health service registers. This method has been described previously in a Danish PhD Thesis.
It should be possible to implement this model, possibly with further modification, in all Danish Counties and thereby ensure quality assurance of the predominant part of diabetes treatment in Denmark.

7.2 Local monitoring and quality assurance

Apart from establishing a national clinical database, systems should be established in the individual departments and individual general practices to identify all diabetes patients in the unit as well as monitor the quality of the treatment. An essential requirement in this connection is that the relevant information is registered in direct connection with the consultation and that this is done without prolonging or affecting the actual consultation. These requirements are best met through the use of electronic patient case notes (although these are as yet only in use at very few diabetes units in Denmark) or through special diabetes databases, of which the one most widespread in Denmark is DiabetesRask. It is not sufficient solely to establish electronic patient case notes or diabetes databases. Each individual department has also to allocate the necessary resources for data analysis and for implementation of necessary changes identified by the monitoring and quality assurance.
8 Prevention of Type 2 diabetes

Optimal prevention of late diabetic complications would naturally entail prevention of the disease itself. The present HTA Project Group has therefore chosen to further examine the studies that elucidate this aspect. The chapter is not to be perceived as a HTA of primary prevention, but rather as a brief review of the most recent literature in the area – a chapter that provides an insight into the perspectives of primary prevention of Type 2 diabetes.

The incidence of Type 2 diabetes has been increasing, and this development seems to continue. The increased incidence of diabetes is primarily attributable to changed lifestyle characterised by reduced physical activity and an increased incidence of obesity. Obesity probably explains 75% of all Type 2 diabetes (742). In the Nurses’ Health Study (743), in which 84,941 women were followed for 16 years, 3,300 women developed diabetes. The most important predictor of the development of diabetes was overweight. Thus the relative risk of developing diabetes was 39-fold higher with a BMI of 35 and 20-fold higher with a BMI of between 30 and 35 compared with women with a BMI <23. Among women who exercised more than 7 hours a week the risk was halved (RR: 0.48) compared with women who exercised less than 30 minutes, irrespective of weight. Around 90% of all Type 2 diabetes in women could be explained by overweight, a lack of physical activity (<30 min. per day), diet (low content of fibre and polyunsaturated fat and high content of saturated fat), smoking and abstinence from alcohol (<5 g alcohol per day, around half a drink per day). Of this, 87% was accounted for by weight, exercise and diet.

Randomised intervention studies

Based on knowledge of the most important lifestyle-related risk factors for the development of diabetes (overweight, lack of exercise and inappropriate diet), several intervention studies have been undertaken in which the participants at high risk of developing Type 2 diabetes were treated with lifestyle intervention. These studies have all shown very promising results. Thus in “The Finnish Diabetes Prevention Study” (744), 522 overweight persons with impaired glucose tolerance (IGT) were randomised to a control group or to intensive lifestyle intervention intended to reduce weight by 5% or more, total fat to <30% of energy intake and saturated fat to <10% of energy intake, to increase fibre intake to >15 g/1,000 kcal and to attain an individualised level of physical activity exceeding 4 hours/week. During the first year the group had seven consultations with a clinical dietician and thereafter one consultation every three months. In addition, the subjects received individual guidance on how to enhance physical activity based primarily on aerobic physical activity. The control group was given oral and written information on diet and physical activity at the start of the study and thereafter at the annual check-up. During the first year the intervention group lost 4.2 kg (4.7%) as compared with 0.8 kg (0.9%) in the control group (p<0.001). After two years the weight loss was 3.5 kg versus 0.8 kg (p<0.001). After 3.2 years, 11% of the intervention group had developed diabetes compared with 23% of the control group, corresponding to a 58% reduction in the occurrence of diabetes. Alterations in lifestyle also reduced other cardiovascular risk factors such as waist circumference, HDL cholesterol, triglycerides and blood pressure. To prevent a single case of diabetes it was necessary to treat 22 persons for one year.

In the American “Diabetes Prevention Program” (the DPP study), which was discontinued ahead of schedule because significantly fewer persons developed Type 2 diabetes in the intervention groups (lifestyle changes or treatment with metformin), 3,234 persons with IGT were randomised to intensive lifestyle intervention, treatment with metformin 850 mg twice daily or to a control group (318). The metformin group received oral and written information on lifestyle changes in the form of diet and increased exercise, and the information was repeated once per year. The weight loss goal for the intensively treated group was 7% on a hypocaloric diet and enhanced physical activity (>150 min per week). In order to achieve this goal the group underwent 16 outpatient sessions over the first 24 weeks and thereafter individual sessions of 30 to 60 min duration once per month. In addition the participants were offered group education aimed at strengthening the lifestyle changes, as well as a personal physical exercise trainer and a psychologist. All had a “lifestyle coach” who was usually a clinical dietician. If the subject started to gain weight, the programme was intensified. The increase in physical activity and the weight reduction were significantly greater in the lifestyle group than in the metformin and placebo groups. The average weight loss in the lifestyle, metformin and control groups, was 5.6, 2.1 and 0.1 kg, respectively. After 2.8 years the occurrence of manifest Type 2 diabetes was 58% lower in the lifestyle group than in the control group (the estimated cumulative incidence rates at three years were 14.4% versus 28.9%). The difference was even greater in the subjects aged 60 years or older (71% lower cumulative incidence), among other things indicating that high age is no obstacle to lifestyle alteration. With
metformin treatment there was 31% less Type 2 diabetes than in the control group (cumulative incidence 21.7%), primarily in the younger overweight persons. To prevent a single case of diabetes by means of lifestyle intervention it was necessary to treat 6.9 persons for three years. The corresponding figure for metformin was 13.9 persons for three years. The lifestyle intervention has been described in detail in a recent publication (745).

The direct cost to the health service of the metformin treatment and lifestyle intervention were USD 2,542 and USD 2,772 per person per three years, respectively (746). The lifestyle treatment in particular was expensive the first year, whereafter the expenses were less than for metformin treatment (746). When both the direct and the indirect expenses such as lost working time were included in the calculation, the expense for three years of treatment in the metformin group and the lifestyle intervention group was USD 2,412 and USD 3,540, respectively, greater than the expense for the placebo treatment. (746). No cost-benefit calculations have been made in relation to the benefit of postponing or hindering manifest Type 2 diabetes. It should be noted that these are American figures and cannot be directly transferred to a Danish setting. It is also important to note that the lifestyle intervention did not hinder the occurrence of Type 2 diabetes, but only postponed it by approximately three years.

Several other studies have shown that pharmacological treatment can postpone the occurrence of diabetes in high-risk patients with IGT.

In the STOP-NIDDM randomised trial, overweight persons (average BMI 31) with IGT were randomised to either treatment with acarbose 100 mg x 3 daily, which delays/reduces the gastrointestinal uptake of carbohydrates, or placebo (747). The participants were instructed in a weight-reducing diet or isocaloric diet, and were encouraged to exercise regularly. The participants were seen at 3-month intervals. Approximately 25% of the participants did not complete the study; of these, half stopped during the first year. After an average of 3.3 years, 32% of the patients in the acarbose group had developed Type 2 diabetes as compared with 42% in the placebo group (p<0.0001), corresponding to a reduction of the cumulative incidence of Type 2 diabetes of 25%. More persons in the acarbose group reverted to normal glucose tolerance, 35% versus 31%, p<0.0001. After the end of the study the patients were followed for three months without acarbose treatment. During this period, more persons in the former acarbose group progressed to Type 2 diabetes (47 out of 306) than in the placebo group (21 out of 199). To prevent a single case of Type 2 diabetes it was necessary to treat 11 patients for 3.3 years.

It is worth noting that the number of cardiovascular events (coronary disease, cardiovascular death, coronary insufficiency and stroke) was halved in the acarbose group (p=0.03), and that the number of patients who developed hypertension was reduced by 34% (p=0.004) compared with the control group (748). It was particularly the risk of developing myocardial infarct that was reduced (RR: 0.09, p=0.02).

Insulin resistance is one of the primary defects that causes diabetes. The glitazones reduce insulin resistance. In the TRIPOD study, 235 women without diabetes who had had gestational diabetes were randomised to treatment with troglitazone or placebo (749). After 30 months of treatment the occurrence of Type 2 diabetes was 56% less in the glitazone group (annual incidence was 12.3% versus 5.4%, 15 patients need to be treated for 1 year to prevent one case of diabetes). This study illustrates that medical treatment aimed at enhancing insulin sensitivity and thereby relieving the insulin-producing cells can reduce the occurrence of diabetes.

In a post hoc analysis of three double-blind, randomised, placebo-controlled orlistat studies of 2-years duration encompassing 675 overweight patients randomised to orlistat 120 mg x 3 daily or placebo combined with a hypocaloric diet (500 to 800 kcal/day) with approx. 30% fat the first year and isocaloric diet the second year, glucose status was estimated by means of an oral glucose tolerance test (750). The weight loss in the orlistat group was 6.7 kg as compared with 3.8 kg in the placebo group. By the end of the studies glucose status had normalised in 72% of the patients with IGT as compared with 49% of the corresponding subjects in the placebo group (p<0.05). Among the patients with IGT, 3% had developed diabetes by the end of the study compared with 7.6% of the placebo group.

The longest and largest randomised intervention study is XENDOS, which took/lasted four years. Obese patients (n=3,300) with a BMI ≥30, and aged between 30 and 60 years (average 43.7 years), of whom 21% had IGT, were randomised to an intensive lifestyle programme (where they were seen every second week for six months and hereafter once a month) plus concomitant treatment with either orlistat or placebo. The study was completed by 799 patients in the orlistat group (52%) as compared with 564 patients in the
placebo group (34%). After one year the orlistat group had lost 10.6 kg relative to 6.2 kg in the placebo group. After four years the figures were 5.8 kg versus 2.8 kg, i.e. a difference of 3.0 kg. For each group as a whole, i.e. both patients with and without IGT, the cumulative incidence of Type 2 diabetes was 6.2% in the orlistat group as compared with 9.0% in the placebo group, corresponding to a risk reduction of 37% i.e. 36 subjects need to be treated for 4 years to prevent one case of diabetes. Considering only the patients with IGT the corresponding figures for cumulative incidence were 18.8% versus 28.8%, yielding a risk reduction of 45% i.e. 10 subjects need to be treated for 4 years to prevent one case of diabetes. In contrast, the incidence of manifest Type 2 diabetes following 4 years treatment of subjects with normal glucose tolerance at the time of randomisation did not differ between the orlistat and placebo groups (2.6% versus 2.7%). Waist circumference, LDL cholesterol and blood pressure were all reduced significantly more in the orlistat group than in the placebo group.

The above-mentioned studies show that lifestyle changes, which often need to endure for many years (perhaps for life) require intensive individual follow-up. Moreover, it is characteristic that the dropout rate is high in lifestyle change studies – approx. 50% after three years. It is unclear how a less motivated group – compared with persons who are so enthusiastic that they will participate in clinical studies – will react to lifestyle changes. In many high-risk groups it is difficult to change physical activity and diet due to cultural and social traditions. Finally, it should be remembered that these studies were undertaken at hospitals with a tradition for undertaking scientific studies, and hence at centres where it was guaranteed that the intervention would be effective and correctly performed. To transfer actual findings to routine practice is a great challenge as the necessary possibilities are not available in the Danish healthcare system at present. This applies with respect to initial help achieving lifestyle changes and to the subsequent follow-up as the effect of lifestyle changes rapidly dissipated when intervention ceases (751).

From intervention studies to practical implementation

Identification of risk groups

Despite the increasing occurrence of Type 2 diabetes there are far more persons in all age groups that do NOT have diabetes than who have the disease. In by far the majority of the studies that have been carried out the subjects have been selected as having a markedly high risk of developing diabetes. As the target group, most studies have therefore focussed on persons with IGT. Moreover, several studies have further required that the person should have IGT on several consecutive occasions. Persons selected in this way have a very high risk of developing diabetes (5-10% per year).

Persons with IGT can only be identified by means of an oral glucose tolerance test. This test lasts two hours during which the person cannot do anything else, and it is relatively costly for both the individual and for society. As persons with IGT are completely symptom-free, they can only be detected through population screening, and there are no methods for identifying high-risk individuals such as exist for Type 2 diabetes. There is no documentation that population screening for IGT and subsequent intervention in persons with IGT will have any effect on the total incidence of the disease (see more in Chapters 2 and 3 on Diagnosis and Screening).

Intervention strategy

The strategies recommended to reduce the risk of developing Type 2 diabetes nearly all have the character of general preventative advice that is also of relevance for the prevention of other disease categories, including cardiovascular disease, several types of cancer and joint diseases. Whether a mass strategy for prevention or a focussed high-risk strategy has the greatest impact at the population level is unclear and is presently being investigated, among other means through a large Danish population-based study (752). There is considerable need for research within this area aimed at clarifying the effect of the various forms of intervention on the risk of developing the disease, but also on the associated costs in the form of economic consequences, consequences for the participants in the form of stress, anxiety and quality of life, and finally the possible rub-off effects on other campaigns or screening programmes if the focus on this area is really enhanced. Lifestyle changes also have effect on cardiovascular risk factors.

The alternative is pharmacological treatment where price and side effects of long-term treatment of “healthy” persons should be taken into consideration.

Until more data are available the focus should be on programmes based on lifestyle changes at both the individual and the national levels – programmes that prevent obesity and hence Type 2 diabetes.
9 Annexes

1) Brief description of the literature search
2) Evidence levels and recommendation grades
3) Description of three different diagnostic models for diagnosing Type 2 diabetes
4) Unit costs for various diabetes-related services
5) Overview of studies of the effect of self-monitoring of glucose in blood or urine in Type 2 diabetes
6) Studies elucidating the effect of physical exercise in Type 2 diabetes patients
7) Current organisation of diabetes treatment in various Danish counties
8) The Aarhus County diabetes register
9) Model of health economic cost-effectiveness analysis of screening for diabetic retinopathy in Type 2 diabetes
10) Transition probabilities used in the model for screening for diabetic retinopathy
11) Sensitivity analyses of the model for screening for diabetic retinopathy.
Annex 1

Short descriptions of the literature search

The search strategies are summarised below. The actual literature reports with detailed descriptions of search strategies and results can be requested from DACEHTA.

**Chapters 2 and 3: Diagnosis upon suspicion of Type 2 diabetes/Screening for Type 2 diabetes**

**Information sources**

MEDLINE, EMBASE, The Cochrane Library, HTA Database, BIOSIS, PsycINFO, DARE, CINAHL, Sociological Abstracts, Danish Cancer Society, Danish Diabetes Association, Danish Heart Association, Diabetes UK, American Diabetes Association, Danish Council of Ethics, DSI Bib, NHS Economic Evaluation Database

**Search strategies**

The search was performed using the following controlled and free terms:

**Prognosis and screening/case finding**

Patient/problem: Type 2 diabetes, NIDDM, diabetes mellitus non insulin dependent, screening, early detection, mass screening, high risk screening

Outcome measures: prognosis, morbidity, mortality

**Quality of life and screening/case finding**

Patient/problem: Type 2 diabetes, NIDDM, diabetes mellitus non insulin dependent, screening, early detection

Outcome measures: quality of life

**Screening tests**

Patient/problem: Type 2 diabetes, NIDDM, diabetes mellitus non insulin dependent, screening, early detection, HbA1c, glycosylated haemoglobin, questionnaire, random blood glucose, fasting blood glucose, OGTT, oral glucose tolerance test

Outcome measures: sensitivity, specificity, positive predictive values, negative predictive values

**Screening and psychosocial consequences**

Patient/problem: Type 2 diabetes, NIDDM, diabetes mellitus non insulin dependent, screening, early detection

Outcome measures: attitude to health, psychosocial impact, patient aspect, false negative reactions, false positive reactions, anxiety, depression, repress, stress, somatisation, change of lifestyle/behaviour, quality of life, labelling, absenteeism from work

**Inclusion criteria:** Epidemiological studies and clinical studies

**Chapter 4: Non-pharmacological treatment of Type 2 diabetes**

**Information sources**


**Search strategies**

The search was performed using the following controlled and free terms:

**Dietary change, weight loss, physical exercise, smoking cessation, foot care**

Patient/problem: Type 2 diabetes, NIDDM and diabetes mellitus non insulin dependent

Intervention (dietary change, weight loss, exercise): diet, dietary habits, dietary intervention, weight reduction, exercise, physical training, physical activity
Intervention (smoking cessation): smoking cessation, antismoking advice
Intervention (foot care): foot care program
Outcome measures: glycaemic control, fasting blood glucose, HbA1c, blood pressure control, lipid profile (cholesterol, triglycerides), weight reduction, BMI, morbidity, mortality, quality of life, patient satisfaction, knowledge attitudes, dietary adherence, healthcare utilization, incidence of hospitalization, economic measures, cost effectiveness, reinforcement, physical activity, late diabetic complication (retinopathy, nephropathy, neuropathy), foot care behaviours, foot ulcer, amputation, peripheral vascular surgery, self-care skills, smoking habits

Self-monitoring of blood glucose, self-management/self-care
Patient/problem: Type 2 diabetes, NIDDM and diabetes mellitus non insulin dependent
Intervention: self-management training
Outcome measure: glycaemic control, hypertension, lipid profile, self-care skills, coping skills (i.e. hyperglycaemia, stress, chronic disease), knowledge, attitudes, dietary adherence, life behaviours, psychological outcome, morbidity, mortality, quality of life, patient satisfaction, compliance (self-reported monitoring), healthcare utilization, incidence of hospitalization, economic measures, cost effectiveness, reinforcement, physical activity

Shared care
Diabetes, organisation, shared care

Inclusion criteria: Human clinical and non-clinical studies in European languages

Exclusion criteria: Case stories

Chapter 5: Pharmacological treatment of Type 2 diabetes

Information sources
MEDLINE, EMBASE, Biological Abstracts, Science Citation Index, OMNI, The Cochrane Library, HSRPROJ, Sociological Abstracts, PsycINFO, Artikelbasen, mRCT, ISTAHC, CRD, DSI Bib, HealthStar, GreyNet, NGC, SBU alert, TIE, SPRILINE, NHS Economic Evaluation Database

Search strategies
The search was performed using various combinations of the following controlled and free terms:

Antidiabetics
Patient/problem: Type 2 diabetes, NIDDM, diabetes mellitus non insulin dependent, patient compliance, patient adherence, attitude to health
Intervention: hypoglycaemic agents, antidiabetics, patient education, health care economics and organizations, costs and cost analysis, NOT cost of illness
Comparison: change of lifestyle, diet therapy, chronic disease, self-care
Outcome measures: mortality, morbidity, quality of life

Lipid-lowering drugs
Patient/problem: Type 2 diabetes, NIDDM, diabetes mellitus non insulin dependent, patient compliance, patient adherence, attitude to health
Intervention: hyperlipidemia, metabolic diseases, patient education, health care economics and organizations, costs and cost analysis, NOT cost of illness
Comparison: change of lifestyle, diet therapy, chronic disease, self-care
Outcome measures: mortality, morbidity, quality of life

Antihypertensive drugs
Patient/problem: Type 2 diabetes, NIDDM, diabetes mellitus non insulin dependent, patient compliance, patient adherence, attitude to health
Intervention: antihypertensive agents, patient education, health care economics and organizations, costs and cost analysis, NOT cost of illness
Comparison: change of lifestyle, diet therapy, chronic disease, self-care
Outcome measures: mortality, morbidity, quality of life
Anticoagulants
Patient/problem: Type 2 diabetes, NIDDM, diabetes mellitus non insulin dependent, patient compliance, patient adherence, attitude to health
Intervention: anticoagulants, patient education, health care economics and organizations, costs and cost analysis, NOT cost of illness
Comparison: change of lifestyle, diet therapy, chronic disease, self-care
Outcome measures: mortality, morbidity, quality of life

Combinations of the above
Patient/problem: Type 2 diabetes, NIDDM, diabetes mellitus non insulin dependent, patient compliance, patient adherence, attitude to health
Intervention: hypoglycaemic agents, antidiabetics, hyperlipidemia, antihypertensive agents, anticoagulants, patient education, health care economics and organizations, costs and cost analysis NOT cost of illness
Comparison: change of lifestyle, diet therapy, chronic disease, self-care
Outcome measures: mortality, morbidity, quality of life

Inclusion criteria: Epidemiological and clinical studies; articles in European languages
Exclusion criteria: Case reports

Chapter 6: Diagnosis and screening for late complications of Type 2 diabetes

Information sources
MEDLINE, EMBASE, Healthstar, Science Citation Index, Social Science Citation Index, PsycINFO, CINAHL, The Cochrane Library, DARE, NHS Economic Evaluation Database, HTA Database, Danish Diabetes Association, Danish heart Association, American Diabetes Association, DSI Bib

Search strategies
The search was performed using various combinations of the following controlled and free terms:

Retinopathy
Patient/problem: Type 2 diabetes, NIDDM and diabetes mellitus non insulin dependent
Intervention: screening, early detection, mass screening, high risk screening
Outcome measures: vision, blindness, diagnosis, morbidity, predictive value of tests, patient compliance, cost effectiveness

Nephropathy
Patient/problem: Type 2 diabetes, NIDDM and diabetes mellitus non insulin dependent
Intervention: screening, early detection, mass screening, high risk screening
Outcome measures: kidney failure, genetic predisposition to disease (genetic markers), glomerular filtration rate, blood glucose, nephrosclerosis, microalbuminuria, hypertension, diagnosis, morbidity, predictive value of tests, patient compliance, cost effectiveness

Ischaemic heart disease and stroke
Patient/problem: Type 2 diabetes, NIDDM and diabetes mellitus non insulin dependent
Intervention: screening, early detection, mass screening, high risk screening
Outcome measures: hypertension, lipid profile, angina pectoris, acute myocardial infarction, weight reduction,physical activity, glycaemic control, smoking, impotence, diagnosis, morbidity, predictive value of tests, patient compliance, cost effectiveness

Neuropathy
Patient/problem: Type 2 diabetes, NIDDM and diabetes mellitus non insulin dependent
Intervention: screening, early detection, mass screening, high risk screening
Outcome measures: neuropathy, impotence, bladder control, diagnosis, morbidity, predictive value of tests, patient compliance, cost effectiveness
Diabetic foot ulcers
Patient/problem: Type 2 diabetes, NIDDM and diabetes mellitus non insulin dependent
Intervention: screening, early detection, mass screening, high risk screening
Outcome measures: diabetic foot (complications), skin care, diagnosis, morbidity, predictive value of tests, patient compliance, cost effectiveness

Inclusion criteria: Epidemiological studies and clinical studies
## Annex 2

### Evidence levels and recommendation grades

<table>
<thead>
<tr>
<th>Grade of Recommendation</th>
<th>Level of evidence</th>
<th>Therapy/Prevention, Aetiology/Harm</th>
<th>Prognosis</th>
<th>Diagnosis</th>
<th>Economic analysis</th>
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<tbody>
<tr>
<td><strong>A</strong></td>
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<tr>
<td>1a</td>
<td>SR (with homogeneity*) of RCTs</td>
<td>[SR (with homogeneity*) of inception cohort studies; or a CPG validated on a test set]</td>
<td>SR (with homogeneity*) of Level 1 diagnostic studies; or a CPG validated on a test set</td>
<td>SR (with homogeneity*) of Level 1 economic studies</td>
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<tr>
<td>1b</td>
<td>Individual RCT (with narrow confidence interval)</td>
<td>Individual inception cohort study with ≥80% follow-up</td>
<td>Independent blind comparison of an appropriate spectrum of consecutive patients, all of whom have undergone both the diagnostic test and the reference standard</td>
<td>Analysis comparing all (critically-validated) alternative outcomes against appropriate cost measurement, and including a sensitivity analysis incorporating clinically sensible variations in important variables</td>
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<tr>
<td>1c</td>
<td>All or none case-series</td>
<td>All or none case-series</td>
<td>Absolute SpPins and SnNouts</td>
<td>Clearly as good or better, but cheaper. Clearly as bad or worse but more expensive. Clearly better and worse at the same cost</td>
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<td><strong>B</strong></td>
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<tr>
<td>2a</td>
<td>SR (with homogeneity) of cohort studies</td>
<td>SR (with homogeneity) of either retrospective cohort studies or untreated control groups in RCTs</td>
<td>SR (with homogeneity) of Level ≥2 diagnostic studies</td>
<td>SR (with homogeneity) of Level ≥2 economic studies</td>
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<tr>
<td>2b</td>
<td>Individual cohort study (including low quality RCT; e.g., &lt;80% follow-up)</td>
<td>Retrospective cohort study or follow-up of untreated control patients in an RCT; or CPG not validated in a test set</td>
<td>Independent blind comparison but either non-consecutive patients, or confined to a narrow spectrum of study individuals (or both), all of whom have undergone both the diagnostic test and the reference standard; or a diagnostic CPG not validated in a test set</td>
<td>Analysis comparing a limited number of alternative outcomes against appropriate cost measurement, and including a sensitivity analysis incorporating clinically sensible variations in important variables</td>
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<td>&quot;Outcomes&quot; Research</td>
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<tr>
<td>4</td>
<td>Case-series (and poor quality cohort and case-control studies)</td>
<td>Case-series (and poor quality prognostic cohort studies)</td>
<td>Reference standard was not applied to all study patients</td>
<td>Analysis without accurate cost measurement; but including a sensitivity analysis incorporating clinically sensible variations in important variables</td>
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<tr>
<td>5</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or &quot;first principles&quot;</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or &quot;first principles&quot;</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or &quot;first principles&quot;</td>
<td>Expert opinion without explicit critical appraisal, or based on economic theory</td>
<td></td>
</tr>
</tbody>
</table>

Levels of Evidence and Grades of Recommendations’ of 18 September 1998 by the Centre for Evidence-Based Medicine in Oxford. The ratings were revised in 2001, cf. [http://www.cebm.net/levels_of_evidence.asp](http://www.cebm.net/levels_of_evidence.asp), but the changes do not affect the evidence levels assigned in the present report. See also Section 1.3.

Type 2 diabetes. Health Technology Assessment of screening, diagnosis and treatment
Annex 3

Description of three different diagnostic models for diagnosis of Type 2 diabetes

The diagnosis of diabetes can be fully or partially carried out in general practice or at a central laboratory. The advantage of carrying it out in general practice is that it is patient-near compared with a central laboratory, which means that the patient does not use unnecessary transport time, thereby reducing the indirect costs. This will be even more pronounced in the more sparsely populated areas of Denmark.

Three different diagnostic strategies have been established where either fasting blood glucose (FBG) or fasting plasma glucose (FPG) are measured. If measurement of fasting glucose reveals that the person has “impaired fasting glycaemia” (IFG), an oral glucose tolerance test (OGTT) is performed. The number of persons passing through each step of the diagnostic strategy has been calculated on the basis of figures from an as yet unpublished pilot study under the ADDITION study.

Model 1 (Figure 1)
In this model all of the diagnosis is carried out in general practice. Measurement of full-blood glucose (capillary glucose) is used as this can be immediately analysed with patient-near equipment, and the patient can thus receive the result immediately

Consultation 1:
The patient presents fasting for the measurement of fasting blood glucose (FBG). If:

- FBG<5.5 mmol/l (normal), the patient does not have diabetes.
- FBG≥6.1 mmol/l, the patient might have diabetes and should therefore report for a second consultation to have the diagnosis verified.
- FBG 5.5-6.0 mmol/l, an OGTT is carried out, possibly in immediate connection with the consultation. If:
  - 2-hr plasma glucose <11.1 mmol/l, the patient does not have diabetes.
  - 2-hr plasma glucose ≥11.1 mmol/l, the patient might have diabetes and should report for a confirmative blood test on another day.

Consultation 2:
Patients with FBG≥6.1 mmol/l or 2-hr blood glucose ≥11.1 mmol/l at the first consultation present fasting for measurement of FBG. If:

- FBG<5.5 mmol/l (normal), the patient does not have diabetes.
- FBG≥6.1 mmol/l, the patient has diabetes, as two diabetic blood glucose concentrations have been measured on two independent days.
- FBG 5.5-6.0 mmol/l, an OGTT is performed, possibly in immediate connection with the consultation. If:
  - 2-hr plasma glucose <11.1 mmol/l, the patient does not have diabetes.
  - 2-hr plasma glucose ≥11.1 mmol/l, the patient might have diabetes and should report for a confirmative blood test on another day.

Resource consumption:
At the 1st consultation all the patients (100%) have FBG measured. Of these, 3% will have a diabetic FBG, 7% will have FBG of 5.5-6.0 and should undergo an OGTT, and 1% will have a diabetic 2-hr value. The first consultation will take 15 min for 93% of the population and 2.5 hours for 7% of the population

At the second consultation, 4% of the patients require FBG measurement, and 1% require an OGTT. The time consumption will be 15 min for 3% of the population and 2.5 hours for 1% of the population.

Model 2 (Figure 2)
In this model the blood samples are taken and prepared in general practice and forwarded to and analysed at a central laboratory. Full venous blood samples are collected, cold-centrifuged and pipetted off within 10 min. This means that the patient will not get the result the same day, but will have to call for the result and possibly thereafter make an appointment for an OGTT.
Consultation 1:  
The patient presents fasting for measurement of fasting plasma glucose (FPG). He/she can then call for the result of the blood test 2-3 days later, whereafter a decision is made as to whether an OGTT is required, or whether the patient should report for a confirmative diagnostic consultation. If:

- FPG<6.1 mmol/l (normal), the patient does not have diabetes.
- FPG≥7.0 mmol/l, the patient might have diabetes and should therefore report for a second consultation in order to have the diagnosis verified.
- FPG 6.1-6.9 mmol/l, an OGTT is required. The patient should present fasting for the OGTT on another day (Consultation 2).

Consultation 2:
All patients with FPG 6.1-6.9 present fasting for an OGTT. If:

- 2-hr plasma glucose <11.1 mmol/l, the patient does not have diabetes.
- 2-hr plasma glucose ≥11.1 mmol/l, the diagnosis diabetes cannot be excluded, and the patient should report for a second, confirmative consultation on another day.

Consultation 3:
All patients with FPG ≥7.0 mmol/l or 2-hr plasma glucose ≥11.1 mmol/l should present fasting for measurement of FPG. The result will not be available until 2-3 days later. If:

- FPG<6.1 mmol/l, the patient does not have diabetes.
- FPG≥7.0 mmol/l, the patient has diabetes.
- FPG 6.1-6.9 mmol/l, an OGTT is required. The patient should present fasting for the OGTT on another day (Consultation 4).

Consultation 4:
All patients with FPG 6.1-6.9 present fasting for an OGTT. If:

- 2-hr plasma glucose <11.1 mmol/l, the patient does not have diabetes.
- 2-hr plasma glucose ≥11.1 mmol/l, the patient has diabetes.

Resource consumption:
100% of the population have a 1st consultation, 7% have a 2nd consultation, 4% a 3rd consultation, and 1% a 4th consultation.

The time consumption is 15 min each for consultations 1 and 3, and 2.5 hours each for consultations 2 and 4.

**Model 3 (Figure 3)**
In this model the whole of the diagnosis is performed at a central laboratory. This strategy assumes that plasma glucose is measured.

Consultation 1:
The patient presents fasting at the central laboratory for measurement of FPG and waits at the laboratory for the result (it takes approx. 1 hour). If:

- FPG<6.1 mmol/l (normal), the patient does not have diabetes.
- FPG≥7.0 mmol/l, the patient might have diabetes and should therefore report for a second test in order to have the diagnosis verified.
- FPG 6.1-6.9 mmol/l, an OGTT is performed in immediate connection with the consultation. If:
  - 2-hr plasma glucose <11.1 mmol/l, the patient does not have diabetes.
  - 2-hr plasma glucose ≥11.1 mmol/l, the patient might have diabetes and should report for a confirmative blood test on another day.

Consultation 2:
The patient presents fasting at the central laboratory for measurement of FPG and waits at the laboratory for the result (it takes approx. 1 hour). If:
- FPG < 6.1 mmol/l, the patient does not have diabetes.
- FPG ≥ 7.0 mmol/l, the patient has diabetes according to WHO criteria.
- FPG 6.1-6.9 mmol/l, an OGTT is performed in immediate connection with the consultation. If:
  - 2-hr plasma glucose < 11.1 mmol/l, the patient does not have diabetes.
  - 2-hr plasma glucose ≥ 11.1 mmol/l, the patient has diabetes.

At the 1st consultation FPG is measured in all the patients (100%). Of these, 3% will have a diabetic FBG, 7% will have a FBG 5.5-6.0 and require an OGTT, and 1% will have a diabetic 2-hr value. The first consultation will take a minimum of 1 hour and 15 min for 93% of the population and 3 hours and 15 min for 7% of the population.

At the 2nd consultation, 4% will have FBG measured, and 1% will require an OGTT. The time consumption will be 1 hour and 15 min for 3% of the population and 3 hours and 15 min for 1% of the population.
Figure 1. The complete diagnosis is performed in general practice. Analysis of whole blood (mmol/l):

1. consultation

FBG ≥ 6.1
FBG 5.5-6.0 → OGGT
2 hr BG ≥ 11.1

2. consultation

FBG ≥ 6.1
FBG 5.5-6.0 → OGGT
2 hr BG ≥ 11.1

Type 2 diabetes

Resource consumption:

100% have FBG measured
3% have FBG ≥ 6.1
7% require an OGGT
1% have 2-hr PG ≥ 11.1,
total of 2 blood samples

4% have FBG measured
1% require an OGGT,
total of 2 blood samples

Time consumption for each consultation: 15 min if only FBG is measured – 2.5 hrs if OGGT is performed
Model 2. Combined diagnosis. General practice collects and centrifuges the samples and forwards them to the central laboratory, which analyses the blood plasma (mmol/l):

1st Consultation  2nd Consultation  3rd Consultation  4th Consultation  Type 2-diabetes

- FPG ≥ 7.0
- FPG 6.1-6.9 → OGGT 2 hr PG ≥ 11.1 → FPG ≥ 7.0
- FPG 6.1-6.9
- OGGT 2 hr PG ≥ 11.1

Resource consumption:

- 100% FPG
- 7% OGGT x 2 samples (incl. new FPG)
- 4% FPG
- 1% OGGT

Time consumption for each consultation: 15 min if only FPG is measured – 2.5 hrs if OGGT is performed

* 2nd og 4th consultations only performed if FPG is inconclusive (6.1-6.9)
Model 3. The complete diagnosis is performed at the central laboratory. Analysis of blood plasma (mmol/l):

1st Consultation

- FPG ≥ 7.0
- FPG 6.1-6.9

→ OGTT
   2hr PG ≥ 11.1

2nd Consultation

- FPG ≥ 7.0
- FPG 6.1-6.9

→ OGTT
   2hr PG ≥ 11.1

Type 2 diabetes

At each consultation/OGTT at the central laboratory the patient has to wait 1 hour for the result of the FPG before an OGTT can be performed.

Resource consumption:

100% FPG
93% use minimum
   1 hr 15 min
7% use 3 hr 15 min

7% OGTT

4% FPG
3% use minimum
   1 hr 15 min
1% use 3 hr 15 min

1% OGTT

Reduced compliance due to transport and travelling time. Will vary depending on geographical location.
## Annex 4

### Unit costs

<table>
<thead>
<tr>
<th>Service</th>
<th>Unit cost (DKK)</th>
<th>Service code</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultation, general practice</td>
<td>101.59</td>
<td>0101</td>
<td>Health Insurance administrative guidelines (1 October 2001)</td>
</tr>
<tr>
<td>Telephone consultation, general practice</td>
<td>24.48</td>
<td>0201</td>
<td>Health Insurance administrative guidelines (1 October 2001)</td>
</tr>
<tr>
<td>Blood sample from blood vessel – per consignment</td>
<td>42.84</td>
<td>2101</td>
<td>Health Insurance administrative guidelines (1 October 2001)</td>
</tr>
<tr>
<td>Blood sample from blood, vessel incl. preparation and centrifugation – per consignment</td>
<td>85.68</td>
<td>2601</td>
<td>Health Insurance administrative guidelines (1 October 2001)</td>
</tr>
<tr>
<td>Blood glucose (photometer)</td>
<td>46.76</td>
<td>7136</td>
<td>Health Insurance administrative guidelines (1 October 2001)</td>
</tr>
<tr>
<td>HbA1c</td>
<td>51.00</td>
<td>KPLL 0271</td>
<td>KPLL [Copenhagen General Practitioners’ Laboratory] price list 2001</td>
</tr>
<tr>
<td>Plasma glucose</td>
<td>71.00</td>
<td>KPLL 0256</td>
<td>KPLL [Copenhagen General Practitioners’ Laboratory] price list 2001</td>
</tr>
<tr>
<td>OGTT</td>
<td>232.00</td>
<td>KPLL 0025</td>
<td>KPLL [Copenhagen General Practitioners’ Laboratory] price list 2001</td>
</tr>
<tr>
<td>Outpatient visit</td>
<td>1,507.01</td>
<td></td>
<td>DNG rates 2002, p. 17 (NB: PL 2002)</td>
</tr>
<tr>
<td>Albuminuria, albumin/creatinine ratio (morning urine)</td>
<td>118.00</td>
<td>KPLL 0506</td>
<td>KPLL [Copenhagen General Practitioners’ Laboratory] price list 2001</td>
</tr>
<tr>
<td>Urine test with test strips</td>
<td>11.69</td>
<td>7101</td>
<td>Health Insurance administrative guidelines (1 October 2001)</td>
</tr>
<tr>
<td>Creatinine, serum</td>
<td>20.75</td>
<td>KPLL 0199</td>
<td>KPLL [Copenhagen General Practitioners’ Laboratory] price list 2001</td>
</tr>
<tr>
<td>Cholesterol (total), serum</td>
<td>21.00</td>
<td>KPLL 0181</td>
<td>KPLL [Copenhagen General Practitioners’ Laboratory] price list 2001</td>
</tr>
<tr>
<td>Foot care of diabetes patients, 1 treatment module</td>
<td>47.28</td>
<td></td>
<td>Health Insurance administrative guidelines (1 October 2001)</td>
</tr>
<tr>
<td>Consultation, ophthalmologist (later consultation)</td>
<td>86.49</td>
<td>0130</td>
<td>Health Insurance administrative guidelines (1 October 2001)</td>
</tr>
<tr>
<td>Diagnosis/control of diabetic changes etc., ophthalmologist</td>
<td>186.35</td>
<td></td>
<td>Health Insurance administrative guidelines (1 October 2001)</td>
</tr>
<tr>
<td>Course day for a general practitioner</td>
<td>2,500.00</td>
<td>Danish Medical Association Educational Secretariat. Personal communication, Tina Pind 10.12.01 excl. VAT, not-for-profit</td>
<td></td>
</tr>
<tr>
<td>Day’s salary, general practitioner (estimate)</td>
<td>2,640.00</td>
<td>Estimated as corresponding to leading physicians</td>
<td></td>
</tr>
<tr>
<td>Blood glucose strips</td>
<td>7.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sampling fee, laboratory</td>
<td>52.00</td>
<td>KPLL Fee A</td>
<td>KPLL [Copenhagen General Practitioners’ Laboratory] price list 2001</td>
</tr>
<tr>
<td>Hourly wage</td>
<td>191.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mailing of questionnaires, incl. reminders</td>
<td>11.65</td>
<td></td>
<td>Post Denmark, Sales Department</td>
</tr>
</tbody>
</table>
### Annex 5

#### Overview of studies of the effect of self-monitoring of blood or urine glucose in Type 2 diabetes

<table>
<thead>
<tr>
<th>No.</th>
<th>Source</th>
<th>Method</th>
<th>Number of patients and duration of study</th>
<th>Intervention</th>
<th>Result</th>
<th>Comment</th>
<th>Evidence grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Coster 2000 (UK) [373]</td>
<td>Meta-analysis of work 2-8</td>
<td>N (total)=285 N (control)=278 3-12 months</td>
<td>Measurement versus no measurement B glucose versus U glucose measurement</td>
<td>No effect of self-monitoring</td>
<td>All studies prior to UKPDS, suboptimally designed, undertaken and described</td>
<td>1a</td>
</tr>
<tr>
<td>2</td>
<td>Wing 1986 (USA) [375]</td>
<td>RCT Parallel group</td>
<td>N (intervention)=23 N (control)=22 3 months</td>
<td>B glucose measurement (strips only) No measurement AE + weight reduction programme</td>
<td>No effect of self-monitoring</td>
<td>50% OHA, 50% insulin Block randomisation Dropout rate 10%</td>
<td>1b</td>
</tr>
<tr>
<td>3</td>
<td>Estey 1989 (Canada) [376]</td>
<td>RCT Parallel group</td>
<td>N (intervention)=28 N (control)=25 3 months</td>
<td>+ encouragement to measure B glucose – encouragement to measure B glucose AE + education</td>
<td>No effect of extra encouragement to measure B glucose</td>
<td>Diet alone 38%, OHA 62% Individual randomisation Dropout rate 12%</td>
<td>1b</td>
</tr>
<tr>
<td>4</td>
<td>Fontbonne RCT N (France) [377]</td>
<td>RCT Parallel group</td>
<td>N (intervention)=110 N (control)=54 6 months</td>
<td>B/U glucose measurement (BG monitor/strips) No measurement</td>
<td>No effect of self-monitoring</td>
<td>OHA 100% Individual randomisation Dropout rate 21%</td>
<td>1b</td>
</tr>
<tr>
<td>5</td>
<td>Muchmore RCT N (USA) [380]</td>
<td>RCT Parallel group</td>
<td>N (intervention)=12 N (control)=11 44 weeks</td>
<td>B glucose measurement (BG monitor) No measurement AE + HbA1c feedback</td>
<td>No effect of self-monitoring</td>
<td>Diet alone 26%, OHA 74% Individual randomisation Dropout rate 21%</td>
<td>1b</td>
</tr>
<tr>
<td>6</td>
<td>Fontbonne 1989 (France) [377]</td>
<td>RCT Parallel group</td>
<td>N (intervention)=56 N (control)=54 6 months</td>
<td>B glucose measurement (BG monitor/strips) U glucose measurement (strips)</td>
<td>No difference between B glucose and U glucose measurement</td>
<td>OHA 100% Individual randomisation Dropout rate 21%</td>
<td>1b</td>
</tr>
<tr>
<td>7</td>
<td>Allen 1990 (USA) [378]</td>
<td>RCT Parallel group</td>
<td>N (intervention)=27 N (control)=15 6 months</td>
<td>B glucose measurement (BG monitor) U glucose measurement (strips) AE + education</td>
<td>No difference between B glucose and U glucose measurement</td>
<td>Diet alone 15%, OHA 85% Group randomisation Dropout rate 15%</td>
<td>1b</td>
</tr>
<tr>
<td>8</td>
<td>Miles 1997 (UK) [379]</td>
<td>RCT Cross-over</td>
<td>N (intervention)=58 N (control)=56 6 (2×3) months</td>
<td>B glucose measurement (BG monitor/strips) U glucose measurement (strips) AE + education</td>
<td>No difference between B glucose and U glucose measurement</td>
<td>Diet alone 47%, OHA 53% Weekly “randomisation” Dropout rate 32%</td>
<td>1b</td>
</tr>
<tr>
<td>9</td>
<td>Schiel 1999 (Germany) [384]</td>
<td>Cross-sectional study</td>
<td>N (total)=942 100% insulin</td>
<td>Comparison between frequency of B glucose measurement and HbA1c level</td>
<td>The more frequent the self-monitoring, the lower the HbA1c, but only after structured educational programme</td>
<td>Author: Self-monitoring is useful as an integrated part of diabetes treatment</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>Karter 2001 (USA) [385]</td>
<td>Register study</td>
<td>N (total)=2153 24% insulin+OHA 35% OHA alone 21% diet alone</td>
<td>Comparison between frequency of B glucose measurement and HbA1c level</td>
<td>In all groups 0.4-0.6% lower HbA1c in patients who self-monitor</td>
<td>Author: Self-monitoring is useful as an integrated part of diabetes treatment</td>
<td>2b</td>
</tr>
<tr>
<td>11</td>
<td>Francosi 2001 (Italy) [386]</td>
<td>Questionnaire survey</td>
<td>N (total)=2,855 From 10 out-patient clinics and 103 general practices 20% insulin+OHA</td>
<td>Comparison between frequency of B glucose measurement and HbA1c level</td>
<td>Effect of self-monitoring restricted to insulin-treated patients able to adjust the insulin dosage themselves</td>
<td>Author: Only self-monitoring in the category mentioned. Poor quality of life and higher HbA1c in non-insulin-treated patients who self-monitor</td>
<td>4</td>
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</tbody>
</table>
FIGURE 1. Result of the meta-analysis of the effect of self-monitoring of glycosylated haemoglobin in Type 2 diabetes (373)

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of subjects (intervention/control)</th>
<th>Difference in GHB (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urine or blood monitoring vs. no monitoring</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wing, 1986</td>
<td>23/22</td>
<td>-0.25 (-1.56 to 1.08)</td>
</tr>
<tr>
<td>Estey, 1989</td>
<td>28/25</td>
<td>-0.40 (-0.85 to 0.05)</td>
</tr>
<tr>
<td>Fontbonne, 1989</td>
<td>110/54</td>
<td>0.25 (-0.45 to 0.97)</td>
</tr>
<tr>
<td>Muchmore, 1994</td>
<td>12/11</td>
<td>-0.85 (-2.47 to 0.78)</td>
</tr>
<tr>
<td><strong>Pooled effect</strong></td>
<td></td>
<td>-0.25 (-0.61 to 0.10)</td>
</tr>
<tr>
<td><strong>Blood monitoring vs. urine monitoring</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allen, 1990</td>
<td>27/27</td>
<td>0.0 (-1.60 to 1.60)</td>
</tr>
<tr>
<td>Fontbonne, 1989</td>
<td>56/54</td>
<td>-0.23 (-1.05 to 0.59)</td>
</tr>
<tr>
<td>Miles, 1997</td>
<td>58-56</td>
<td>0.10 (-0.57 to 0.77)</td>
</tr>
<tr>
<td><strong>Pooled effect</strong></td>
<td></td>
<td>-0.03 (-0.52 to 0.47)</td>
</tr>
</tbody>
</table>
### Effekt of physical intervention

<table>
<thead>
<tr>
<th>Year (ref.)</th>
<th>Intervention/Control (n)</th>
<th>Training programme sessions/week, duration/session, intensity</th>
<th>Duration</th>
<th>Significant improvement in condition</th>
<th>Fasting glucose/HbA1c</th>
<th>Fasting insulin</th>
<th>Fasting C peptide</th>
<th>Insulin resistance²⁷</th>
</tr>
</thead>
<tbody>
<tr>
<td>1984 (388)*</td>
<td>10/8</td>
<td>3×/week, 20-30 min., 75% VO₂max</td>
<td>12 weeks</td>
<td>Yes</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓¹⁸</td>
</tr>
<tr>
<td>1985 (392)</td>
<td>33/13</td>
<td>3×/week, 50 min., 80-90% VO₂max</td>
<td>3 months</td>
<td>Yes</td>
<td>↓</td>
<td>←</td>
<td>←</td>
<td>←¹⁹</td>
</tr>
<tr>
<td>1986 (280)</td>
<td>13/12</td>
<td>5-7×/week, 45 min., 70% VO₂max</td>
<td>4 months</td>
<td>Yes</td>
<td>↑↓</td>
<td>←</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>1988 (359)*</td>
<td>10/12</td>
<td>Ordinary walk 3×/week, 60 min., 5 km/hour</td>
<td>6 months</td>
<td>--</td>
<td>←/↔</td>
<td>←</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>1990 (395)</td>
<td>8/8</td>
<td>3×/week, 50-60 min., 60-77% of max. pulse</td>
<td>8 weeks</td>
<td>Yes</td>
<td>↓↓↓</td>
<td>❋</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>1992 (394)</td>
<td>38/40</td>
<td>3-4×/week, 10-60 min., Pulse: 110-140/min</td>
<td>1 year</td>
<td>No</td>
<td>↑</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>1994 (395)</td>
<td>19/19</td>
<td>3×/week, 50-55 min., 65% VO₂max</td>
<td>12 weeks</td>
<td>Yes</td>
<td>↓↓</td>
<td>←</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>1995 (398)</td>
<td>16/13</td>
<td>3×/week, 10-90 min., 50-70% of max. pulse</td>
<td>3 months</td>
<td>Yes</td>
<td>↓↓↓</td>
<td>←</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>1997 (397)*</td>
<td>30/25</td>
<td>3×/week²³, 30 min., –</td>
<td>6 months</td>
<td>–</td>
<td>↓</td>
<td>←</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>1997 (399)</td>
<td>25/26</td>
<td>3×/week, 60 min., 60-80% VO₂max</td>
<td>6 weeks²⁴</td>
<td>Yes</td>
<td>↓↑</td>
<td>←</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>1999 (396)</td>
<td>11/12</td>
<td>3×/week, 30-40 min., 55-65% VO₂max</td>
<td>8 weeks</td>
<td>Yes</td>
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<td>↔</td>
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Studies elucidating the effect of physical exercise in Type 2 diabetes – continued

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<th>Total cholesterol</th>
<th>BP</th>
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<td>↓</td>
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</table>

²⁴ Number of persons.
²⁵ Inclusive any time used for warm-up and stretching out.
²⁶ Measured by hyperinsulinaemic glucose clamp technique or by insulin tolerance test.
²⁷ Effect of exercise, not of diet.
²⁸ By condition is understood improved VO₂-max or decreased pulse response to a given task.
²⁹ Dependent on insulin secretion capacity.
³⁰ No further effect of exercise on any parameters.
³¹ In women, but not in men.
³² Only supervised once per week.
³³ Very variable participation in weekly diet and exercise instructions.
³⁴ Followed by 20 weeks of unsupervised exercise.
³⁵ Reduction of daily insulin dosage.
³⁶ Percentage of fat decreased significantly.
³⁷ In men, but not in women.
³⁸ Percentage of fat decreased significantly.
³⁹ No weight loss, but significantly increased energy intake.
⁴⁰ Magnetic resonance image showed significant decrease in both visceral and subcutaneous abdominal fat, however.
Current organisation of the diabetes treatment in various counties in Denmark

This annex presents organisational models currently in use in various Danish counties.

**Copenhagen County**

In Copenhagen County Type 2 diabetes patients can be referred to diabetes schools established in the County’s three hospitals. Here the patients participate in a structured educational programme. Both newly diagnosed patients and patients with longstanding diabetes in need of instruction can be referred. The primary tasks of the diabetes schools encompass dietary instruction, training in measurement of blood glucose, motivation to smoking cessation, motivation to physical exercise and pharmacological treatment. The diabetes schools have an affiliated nurse, clinical dietician, podiatrist and social worker. Under the agreement, moreover, guidelines have been drawn up for referral, control and treatment as well as for cooperation between the primary and secondary sectors. The proposal also contains a declaration of intent regarding quality assurance. Communication between the diabetes centres and the primary sector is ensured through the exchange of discharge records and outpatient notes. The proposal entails that the general practitioner is the central healthcare professional, while the role of the secondary sector is to support the general practitioner and to deal with the treatment and control of particularly complicated patient groups. To implement the regional diabetes centres, Copenhagen County has allocated DKK 3 million in 2002 to enable the employment of one consultant physician, one nurse and half a clinical dietician at each of the hospitals, as well as the provision of secretarial assistance. It is estimated that the activity will encompass 1,355 patients per year at the three hospitals. The patients are offered six outpatient consultations consisting of two initial consultations, three follow-up consultations and a final consultation with a consultant practitioner, a total of 8,130 outpatient consultations at the three hospitals. After a start-up phase, 1,020 patients per year are expected at each of the three hospitals, corresponding to a total of 6,120 outpatient consultations.

**Funen County**

The “Funen” model builds on the principle that diabetes treatment in both the primary and the secondary sector shall have the same high quality throughout the county. The treatment is decentralised out of consideration for the proximity principle. A total of four diabetes clinics have been established on Funen, all staffed with a full diabetes team. Moreover, a general practice diabetes coordinator has been appointed to coordinate the cooperation between general practice and the diabetes clinic, and clinical dieticians have been appointed solely to advise diabetes patients from general practice. The latter are employed at the diabetes clinics to ensure the professional environment. The dieticians can be contacted directly by the patients independently of doctors and the clinic. Furthermore, patient care notes that follow the patient from hospital to general practice and vice versa have been introduced in order to improve the communication between general practice and the diabetes ambulatories. Foot care clinics have been established in association with the diabetes clinics. The diabetes teams provide education to general practice in the form of courses. Education of visiting healthcare workers, kitchen staff and secretaries employed in general practice has also been established. Practical “patient pathway guidelines” have been drawn up specifying good clinical standards and local agreements in the diabetes area and standards have been drawn up for foot ulcer treatment and clinical dieticians. Moreover, newsletters and an audit project that collects data on diabetes patients have been established. A data consultant has been employed, and in summer 2003, a common electronic web-based diabetes registration system was implemented in the whole of Funen County (The Funen Diabetes Database). The diabetes school, the purpose of which is to teach diabetes patients self-care, also covers theoretical and practical aspects such as shopping and cooking. Moreover, emphasis is placed on changing physical activity and smoking habits among the “pupils”. The school consists of six sessions of 3-6 lessons. The “Funen model” is described in detail in a report by the Funen County Diabetes Committee 1997 (489). Funen County has allocated an annual sum of DKK 3.7 million to the project, primarily for employing staff in the diabetes centres. A subsequent evaluation in October 2000 (available from the Quality and Planning Department, Odense University Hospital) shows that the diabetes treatment has become more outpatient oriented and that the division of responsibilities between general practice and the diabetes clinics has become clearer (753). Five new clinical dieticians have been employed to help in general practice, and more uniform and comprehensive dietary guidance is now given such that this service can now be used directly by the diabetes patient as needed, independently of the diabetes clinics or the patient’s general practitioner. In an analysis of 69 patients referred from general practice to a dietician, the average weight loss after four consultations was 5.1 kg. HbA1c had fallen from 8.22% to 6.78% (−1.44 percentage points) and LDL cholesterol from 3.76 mmol/l to 3.36 mmol/l (−0.40 mmol/l), while HDL cholesterol had increased from 1.13 mmol/l to 1.25 mmol/l, and the triglyceride level had
decreased from 2.20 mmol/l to 1.79 mmol/l without the antidiabetic treatment having been changed. No long-term results are available. Half of the diabetes patients have attended a diabetes school, and nearly all the patients self-monitor their blood glucose. There are better prophylactic measures in relation to complications, including foot ulcers. Sixty-seven percent of the patients regularly see a podiatrist. The latter has led to a fall in the number of amputations. Eighty-seven percent of the general practitioners make an annual assessment of the complications suffered by their patients. Approximately 90% of the patients undergo eye screening once a year. The patients’ self-care has been strengthened. The professionalism of the personnel has been enhanced, and interest in diabetes treatment has increased. One of the goals was to transfer more treatment out into the outpatient system and to focus on prevention in order to reduce the number of hospital admissions, and this seems to have succeeded.

**Roskilde County**

In Roskilde County, general practice and the diabetes clinic have been cooperating for many years with diabetes patients being seen once a year in the diabetes clinic. Moreover, newly diagnosed Type 2 diabetes patients can be referred to the clinic. A general practice consultant is affiliated to the scheme, and general practitioners may freely refer patients to the clinical dieticians, of which two are employed in the county for use in general practice. In Roskilde County, computer generated patient information shows the various variables included in the treatment, e.g. weight, blood pressure, HbA1c and eye status in graph form. The computer system is also used as database – “Diabetes-Rask”. The latter enables pathway analysis to be performed for Type 2 diabetes patients and provides the possibility to ensure that the patients are tested for albuminuria and see an ophthalmologist and come to foot control.

**Frederiksborg County**

Frederiksborg County has also developed an action plan for future treatment of Type 2 diabetes patients that focuses on strengthened self-care based on knowledge and an extended cooperation between the primary and the secondary sectors. The plan also focuses on prophylactic measures against obesity, poor diet and Type 2 diabetes. The county currently has approx. 14,000 Type 2 diabetes patients, of which 8,000 have been diagnosed. The number of diabetes patients will increase by 200-300 per year. The problems in the county are well known: a large number of persons with undiagnosed Type 2 diabetes, too few dieticians, no systematic educational programmes, a lack of cooperation agreements between the primary and secondary sectors, and inadequate quality assurance of the treatment. As a consequence, not all diabetes patients are offered the same treatment possibilities.

The action plan is founded on shared care, the establishment of diabetes schools, a wound centre, a knowledge centre and development of the dietician scheme. The quality assurance includes the use of computer registration, possibly web-based. The plan is detailed, and the total implementation costs are calculated to be DKK 7.3 million. The annual operation costs of diabetes schools are calculated to be DKK 3.7 million. The wound centre is to be established by reassigning the existing resources in the county and will not entail new expenses. A knowledge centre focussing on diabetes (0.5 consultant physician) will cost DKK 0.3 per year, and expansion of the dietician scheme will cost DKK 1.2 million per year. In all, the plan will cost approx. DKK 7.0 million per year when fully implemented in the year 2005. The plan can be obtained from Planning Consultant Bente Skov Bonde, the Planning and Prevention Department, Frederiksborg County Town Hall, Hillerød.

After a pilot project, Frederiksborg County established three new dietician positions with responsibility for general practice. During a project period from January 1998 to July 1999, 282 patients were referred to the dieticians. Of these, 37% had Type 2 diabetes. A weight loss of 3.6 kg was achieved and cholesterol fell by 1.07 mmol/l (14%), LDL cholesterol by 0.6 mmol/l (11%) and HbA1c by 0.91 percentage points (corresponding to 11% of the original value). The patients were satisfied with the scheme, and 90% of the general practitioners stated that they wanted the scheme to be rendered permanent. Expenses for dietary treatment were estimated at approx. DKK 2,000 per patient. The report can be obtained from Clinical Dietician Anne Arentoft, Ved Store Dyrehave 20, 3400 Hillerød.

For further information on how the diabetes treatment is organised in various Danish counties the reader is referred to the 1999 report by the Danish Diabetes Association “Fire forslag til organiseringen af diabetesbehandlingen i Danmark” (Four proposals for the organisation of the diabetes treatment in Denmark). It should be pointed out that apart from the two publications mentioned earlier (333, 574), no published data are available on the effect of specific ways of organising diabetes care on fulfilment of the therapeutic goals or the occurrence of late diabetic complications. In particular, there are no results available regarding the value of non-pharmacological treatment.
Annex 8

The diabetes register for Aarhus County

Monitoring of the Type 2 diabetes population in Aarhus County

The project “Monitoring of the Type 2 diabetes population in Aarhus County” aims to describe the occurrence of Type 2 diabetes in Aarhus County and the risk factors for the development of late complications. A further aim is to compare the management and effect of diabetes care among Type 2 diabetes patients in daily clinical practice with the management and effect of diabetes care in a research project.

An earlier PhD project “Identification of the NIDDM-population and evaluation of control and treatment quality in Vejle County” defined and validated a model for identification of diabetes patients by means of register data. In this model it was important that as many diabetes patients as possible were identified, while concomitantly being correctly classified, i.e. a high sensitivity (91%) combined with a high positive predictive value (95%). The identification of the diabetes population in Aarhus County is based on this model.

The project thus identifies the diabetes population using register data. Information is retrieved about persons who on one or more occasions during the course of a year have been registered in:

1. The County’s health insurance register due to:
   - Prescriptions for insulin and oral antidiabetics.
   - Payments to the primary sector (payments for blood glucose measurement, podiatrist)
2. The County’s laboratory databases due to:
   - Measurement of HbA1c.

The persons identified via the registers are checked in the general practitioner register to identify their general practitioners. The Danish Civil Registration System is used to identify any of these persons who have moved away from the municipality or have died. Data are collected for up-dating the diabetes population each year during the period 2000 to 2005.

Upon identification the diabetics will be classified as follows:

- Type 1: Insulin-treated
- Type 2: Insulin-treated, tablet-treated, diet-treated.

As it is not possible to classify all insulin-treated diabetes patients as Type 1 and Type 2 based on register data alone, supplementary information is obtained with the help of case records from the Ophthalmology Department of Aarhus University Hospital, as well as by means of questionnaires sent to general practitioners and diabetes patients. In these cases the diagnostic criterion for Type 2 diabetes is onset of disease at age >40 years.

Thereafter the identified diabetes population is described with regard to demographic data (age, sex, treatment and control location), morbidity (diabetes, cardiovascular, kidney, eye- and neuropathy-related diagnostic codes, treatment with drugs, including antidiabetics, antihypertensives and lipid-lowering agents, and creatinine level) and the occurrence of risk factors for the development and progression of diabetic late complications (HbA1c, lipids and duration of diabetes).

These data are collected with the aid of:

- Register information (Aarhus County health insurance register, Aarhus County’s laboratory databases, the patient administration system)
- Case records (Ophthalmology Department, Aarhus University Hospital)
- Questionnaires to general practitioners and diabetes patients.
Annex 9

Model of health economic cost-effectiveness analysis of screening for diabetic retinopathy in Type 2 diabetes

A) Schematic overview of the model's overall structure
B) Overview of the population that is not registered and which does not undergo screening.
C) Overview of the population that is registered and which undergoes screening

D) Summary of the population that is registered and which undergoes screening
Annex 10

Transition probabilities used in the model for screening for diabetic retinopathy

Annual transition probabilities

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## Annex 11

### Sensitivity analyses of the model for screening for diabetic retinopathy (costs in DKK)

#### Level 1

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#### Level 2

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#### Level 3

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### Screening False positive Diagnosis and Total Costs in the case incl. fixed costs treatment of health-related of blindness true positive costs

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<td>1,016,402</td>
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### Total costs to society Total QALY No. of saved sight-years Costs per QALY

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References


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