Scottish Intercollegiate Guidelines Network

55 Management of Diabetes

A national clinical guideline

November 2001

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

1^{++}	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2^{++}	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

GRADES OF RECOMMENDATION

A	At least one meta-analysis, systematic review, or RCT rated as 1^{++} and directly applicable to the target population*; or* A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results*; or* Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results*; or* Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4*; or* Extrapolated evidence from studies rated as 2^{+}

GOOD PRACTICE POINTS

☑	Recommended best practice based on the clinical experience of the guideline development group

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Management of Diabetes

This guideline is dedicated to the memory of SIGN's founding chairman, Professor Jim Petrie, CBE.

It was Jim's insight which recognised the importance of a professionally-led national clinical guideline programme for Scotland; his energy, commitment and the irresistible force of his personality which nurtured SIGN to fruition; and his rigorous, challenging intellect which steered its development into the nationally and internationally respected organisation it is today. Amongst his innumerable achievements, both personal and professional, we hope that SIGN will stand as a lasting tribute to Jim's memory.

Jim was an inspirational leader, a wise teacher, and trusted friend to everyone in SIGN. He is greatly missed. But we are thankful that we had the great good fortune to know Jim; and we will continue his work to improve the quality of health care for patients in Scotland and worldwide.

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1 Introduction

1.1 BACKGROUND

Diabetes mellitus is a major and increasing health problem in all age groups in Scotland. Diabetes UK estimates that of a population of 5.2 million in Scotland in the year 2000, 122,900 people had confirmed diabetes mellitus and a further 87,100 were undiagnosed, giving a total of 210,000 people with diabetes. Accurate national prevalence data is unknown, but data from the Tayside Diabetes Registry suggests that the prevalence is over 2.6% and rising. Type 2 diabetes, in particular, is a growing problem with a rapidly increasing prevalence due to the ageing population and the increasing incidence of obesity.[1] It is now being recognised in adolescents and young adults.

Diabetes is still the commonest cause of blindness in the working population. 20-25% of patients entering end-stage renal failure replacement programmes have diabetes. Foot problems are the commonest cause of admission to hospital in patients with diabetes, with a 15-20 fold increased risk of amputation. The life expectancy of a patient with type 2 diabetes is reduced by 8-10 years, and atherosclerotic vascular disease, especially coronary artery disease and stroke, is the principal cause of death in about 70% of these patients. Pregnancy in women with diabetes has a poorer outcome for the fetus than a non-diabetic pregnancy. Children and adolescents with diabetes present difficulties in management, requiring a multidisciplinary team approach.

1.2 REVIEWING THE ORIGINAL SIGN GUIDELINES

The original six SIGN guidelines for diabetes were published in 1996-97 and dealt with visual impairment (SIGN 4), pregnancy (SIGN 9), children and young people (SIGN 10), renal disease (SIGN 11), foot disease (SIGN 12) and cardiovascular disease (SIGN 19). In addition, SIGN published in 1998 a recommended minimum dataset for collection in people with diabetes (SIGN 25).

The guidelines have been widely accepted by all professionals responsible for diabetes care in Scotland and many of the guideline recommendations have been adopted in other countries. However, in keeping with SIGN's commitment to update its evidence-based guidelines in the light of emerging evidence, it was agreed that the original guidelines should be reviewed. This has provided an opportunity to review the remit of the guidelines and a new section dealing with lifestyle has been introduced. The seven aspects of care now covered are published here as one SIGN guideline on diabetes mellitus. Further information, where appropriate, is available from the SIGN website at **www.sign.ac.uk.**

In September 2000, the Working Group on IT to Support Shared Care in Diabetes published a document which laid out principles of support and promotion of integrated care for patients with diabetes and also discussed the data collection required in the clinical management of these patients. This group published an extended dataset, based on SIGN 25, which was felt to be more useful for recording information directly relevant to active clinical care than the SIGN document which was felt to be most useful for population-level registers.[2] For this reason, the SIGN minimum dataset has not been reviewed in this document.

1.3 THE AIM OF THE GUIDELINE

The aim has been to provide an updated evidence-based approach to influence current practice in order to reduce the burden of long-term complications, both microvascular and macrovascular, as well as improve pregnancy outcome for the mother with diabetes. The guideline also incorporates the new World Health Organisation diagnostic criteria for diabetes mellitus which were implemented in the UK in June 2000.

1.4 NATIONAL DIABETES INITIATIVES

The Scottish National Health Plan "Our National Health", published in December 2000 gave a commitment that the Scottish Executive would publish a Scottish Diabetes Framework by the end of 2001. The Clinical Standards Board for Scotland will identify clinical standards for diabetes services. These standards will be fully aligned with the Framework. The revised SIGN diabetes guideline will be the cornerstone of evidence-based clinical practice for the Framework and the standards to move forward the improvement of diabetes care in Scotland.

1.5 DEFINITION AND DIAGNOSIS OF DIABETES MELLITUS

Diabetes mellitus is defined as a metabolic disorder of multiple aetiology characterised by chronic hyperglycaemia with disturbances of carbohydrate, protein and fat metabolism resulting from defects in insulin secretion, insulin action, or both. The clinical diagnosis of diabetes is often indicated by the presence of symptoms such as polyuria, polydipsia, and unexplained weight loss, and is confirmed by measurement of abnormal hyperglycaemia.[3]

WHO[3] advises that the range of blood glucose indicative of diabetes mellitus are as follows:*

- random venous plasma glucose ≥11.1 mmol/l; or
- fasting plasma glucose (FPG) ≥7.0 mmol/l; or
- plasma glucose ≥11.1 mmol/l at two hours after a 75 g oral glucose load (the oral glucose tolerance test (OGTT)).

Although patients with type 1 diabetes usually present with characteristic symptoms and should be immediately referred to specialist diabetes care upon diagnosis, for the asymptomatic individual, at least one additional plasma glucose with a value in the diabetic range above is essential to diagnose diabetes accurately. This may be from a fasting (casual sample) or from an OGTT.

1.6 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of clinical care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made in light of the clinical data presented by the patient and the diagnostic and treatment options available. However, it is advised that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

1.7 REVIEW AND UPDATING

This guideline was issued in 2001 and will be considered for review in 2004, or sooner if new evidence becomes available. Any updates to the guideline will be noted on the SIGN website: **www.sign.ac.uk.**

**Impaired Glucose Tolerance (IGT) is a stage of impaired glucose regulation (FPG < 7.0 mmol/l and OGTT 2 hour value ≥ 7.8 mmol/l but < 11.1mmol/l).*

Impaired Fasting Glycaemia (IFG) has been introduced to classify individuals who have fasting glucose values above the normal range but below those diagnostic of diabetes. (Fasting plasma glucose ≥6.1 mmol/l but < 7.0 mmol/l).

IGT and IFG are not clinical entities in their own right, but rather risk categories for cardiovascular disease (IGT) and/or future diabetes (IFG).

2 Children and young people with diabetes

The following recommendations are for all health professionals who advise and support children and young people with diabetes and their families. They should be used in combination with other recent practice guidance, particularly the International Society for Paediatric and Adolescent Diabetes Consensus Guidelines, 2000.[4] There is no agreed definition of what is meant by a young person in this context. Various age ranges have been used in the literature.

2.1 DIAGNOSIS AND EPIDEMIOLOGY

Diabetes is the most common metabolic disease in the young. The Scottish Study Group for the Care of the Diabetes in the Young has shown that currently there are nearly 2,000 people with diabetes aged under 16 years in Scotland, with an annual incidence of 25 per 100,000 population and a near tripling of new cases in the last 30 years.[5] Type 1 diabetes, resulting from beta-cell destruction and absolute insulin deficiency, accounts for over 90% of diabetes in young people aged less than 25 years, and is autoimmune in origin. Non-type 1 diabetes is being recognised with increasing frequency, particularly emerging molecular forms of diabetes, diabetes secondary to pancreatic disease, and a rise in type 2 diabetes and other insulin resistance syndromes in the young.[6]

2.1.1 TYPE 1 DIABETES

12-15% of young people under the age of 15 years with diabetes mellitus have an affected first degree relative (a positive family history).[7] Children are three times more likely to develop diabetes if their father has diabetes rather than their mother.[8] While there are known antibody markers of prediction in high risk subjects, there is no evidence for effective methods of prevention of diabetes.[9] Screening is considered unethical except in the context of a trial. There are several randomised trials in progress (e.g. ENDIT, DPT-1, DIPP) investigating different therapies for the prevention of type 1 diabetes. It is anticipated that results will be available in the next five years. 2++

B **Screening for pre-type 1 diabetes is not recommended in either the general population or in high risk children and young people.**

2.1.2 CYSTIC FIBROSIS AND DIABETES

20% of patients with cystic fibrosis will develop secondary diabetes by the age of 20, with an incidence which increases to 80% by the of age 35.[10] Limited data suggest that clinical symptoms deteriorate when diabetes develops in cystic fibrosis,[11,12] although no evidence exists that the presence of diabetes or its treatment affects long term survival. 2+

C **Patients with cystic fibrosis should be screened annually for diabetes from 10 years of age.**

2.2 INITIATING THERAPY AT DIAGNOSIS

Home-based instruction of the newly diagnosed child or young person appears to be at least as effective as inpatient instruction in terms of glycaemic control and family acceptability over a two-year period.[13] Management in the community using a home-based education programme for patients with newly diagnosed diabetes has been shown also to be cost-effective.[14,15] 2+

C **A home-based programme for initial management and education of children with diabetes and their families is an appropriate alternative to a hospital-based programme.**

The evidence on the role of intensive initial therapy to achieve normoglycaemia as rapidly as possible is inconsistent. In particular, there is no evidence of a sustained effect of any specific insulin therapy on glycaemic control during the first few months after diagnosis. Therefore, no recommendation can be given for the most appropriate insulin therapy at diagnosis.

2.3 CONTINUING MANAGEMENT

There is at present no evidence for the effectiveness of any medication other than insulin in the management of type 1 diabetes in the young.

☑ Medications other than insulin presently have no role in the management of type 1 diabetes in young people.

2.3.1 INSULIN REGIMEN

Conventional therapy for type 1 diabetes (twice daily insulin with support from a multidisciplinary healthcare team and regular diabetes and health monitoring) is associated with variable results.[7]

Limited data support an improvement in glycaemic control using three rather than two injections per day.[7,16,17] 2+

Evidence regarding the impact of an intensive insulin regimen on long term control is derived principally from the Diabetes Control and Complications Trial (DCCT) which also involved a comprehensive patient support element (diet and exercise plans, monthly visits to the health care team, etc).[18,19] Intensive insulin therapy (four injections or more per day or pump insulin) significantly improves glycaemic control over a sustained period compared with conventional insulin therapy (two injections per day). DCCT did not include children aged less than 13 years and, due to the study design, it is impossible to separate the benefits of intensive insulin therapy from intensive support. 1+

B **Intensive insulin therapy should be delivered as part of a comprehensive support package.**

While there is no evidence on the most effective form of support package, in general this refers to increased contact between patients and their families with a local multidisciplinary team of health professionals delivering specific health care strategies.

The risk of hypoglycaemia increases with intensive therapy,[18,19] but rapid acting insulin analogues, as part of a three or four injection regimen can reduce hypoglycaemia.[20,21,22] 1+, 2+

C **The insulin regimen should be tailored to the individual child to achieve the best possible glycaemic control without disabling hypoglycaemia.**

☑ Post-prandial analogue insulin may safely be used in very young children with unpredictable eating patterns.

2.3.2 DIETARY MANAGEMENT

A regimen which includes dietary management has been shown to improve glycaemic control.[18,19] Limited evidence was identified concerning the optimal type of dietary therapy.[23] There is a lack of evidence to recommend either a qualitative or quantitative approach as the most effective mode of dietary therapy. 1+, 2+

B **Dietary advice as part of a comprehensive management plan is recommended to improve glycaemic control.**

☑ Specialist dietetic advice should be given by a dietitian with expertise in childhood diabetes, wherever possible.

2.4 PSYCHOLOGICAL INTERVENTIONS

Factors contributing to an increased risk of young people with diabetes developing psychological problems include: 2+

- avoidance coping (strategies which do not actively try to solve a difficulty faced)[24]
- too much responsibility on the child[24]
- family conflict[24]
- lack of communication, both within families and with the diabetes team[25]

- low socio-economic status[25]
- non-traditional family structure[26]
- poor maternal health, especially depression.[27]

2+

Eating disorders are more common in adolescents with diabetes compared with non-diabetic peers, and adversely affect glycaemic control.[28,29]

2++

B **Regular assessment for psychological problems, especially maladaptive coping strategies and eating disorders is recommended.**

Specific psychological problems (e.g. maladaptive coping strategies) linked to future glycaemic control, can be identified at diagnosis and 1-2 years later, using validated tools performed by a trained practitioner.[30]

Psychological or educational interventions have positive effects on psychological outcomes, knowledge about diabetes and glycaemic control.[31] Maintaining parental involvement improves glycaemic control.[32,33]

2++

Interventions which promote diabetes-specific coping skills are effective and add to the effectiveness of intensive management.[34,35]

1+

A **The use of cognitive coping strategies targeted at diabetes-specific problems is recommended.**

B **Parental support and family communication should be encouraged, with targeted psychological treatment of family disruption and related stress factors.**

2.5 LONG TERM COMPLICATIONS AND SCREENING

2.5.1 RISK OF MICROVASCULAR COMPLICATIONS

Early abnormalities in children and adolescents (e.g. microalbuminuria, background retinopathy) predict later development of long term microvascular complications.[18,19,36,37]

2+

Maintaining glycaemic control to as near normal as possible significantly reduces the long term risk of microvascular diseases.[18,19] Poor glycaemic control (HbA_{1c}>10%) over time in young people with diabetes increases the risk of the development of retinopathy by approximately eightfold.[19]

1+

A **To reduce the risk of long term microvascular complications, the target for all young people with diabetes is the optimising of glycaemic control towards a normal level.**

2.5.2 SCREENING FOR EARLY SIGNS OF MICROVASCULAR DISEASE

The literature is confusing in relation to the timing of commencing screening in young people with diabetes. Age and puberty are reported without any strict definition. For clarity and simplicity the guideline development group suggests 12 years of age in both boys and girls.

Early microvascular abnormalities may occur before puberty, which then appears to accelerate these abnormalities.[38]

2+

Several cohort studies demonstrate the ability to detect the following in young people with diabetes:

- retinopathy (by ophthalmoscopy or fundal photography)[39]
- microalbuminuria (by albumin excretion rate (AER) or albumin/creatinine ratio (ACR))[40-42]
- hypertension.[43-45]

2+, 3

C **Young people with diabetes should receive examination of the retina annually from the age of 12 years.**

C **Young people with diabetes should have their urine microalbuminuria (overnight AER or first morning ACR) tested annually from the age of 12 years.**

D **Blood pressure should be measured annually in young people with diabetes from the age of 12 years.**

☑ Young people with diabetes who have abnormal recorded levels of microalbuminuria or hypertension should make intensive efforts to optimise glycaemic control to minimise progression to microvascular disease.

There is no evidence that routine screening for autonomic neuropathy or hyperlipidaemia are of benefit.

2.5.3 ASSOCIATED CONDITIONS

Thyroid and coeliac disease are reported to be increased in young people with type 1 diabetes compared with non-diabetic subjects.[46-48] Both thyroid and coeliac disease may occur with minimal symptoms that may be missed during routine care. 2+

C **Young people with diabetes should be screened for thyroid and coeliac disease at onset of diabete sand at intervals throughout their lives.**

Standard blood tests exist to screen for thyroid and coeliac disease, but there are limited data to support the specific frequency of screening.

3 Lifestyle management

Modification of adverse lifestyle factors is an important aspect of the management of both type 1 and type 2 diabetes. In particular, appropriate management of cardiovascular risk factors such as smoking, physical inactivity and poor diet is important for the prevention of macrovascular disease. Microvascular complications may also be affected by adverse lifestyle factors e.g. smoking. However, helping patients to modify certain behaviours must take account of other factors, such as the patients' willingness to change, their perception of their diabetes, and other factors which may be related to their diabetes, such as depression and adverse effects on quality of life.

This section of the guideline has been divided into the following areas: delivery of lifestyle interventions; self-monitoring; quality of life and depression; and the specific areas of smoking, physical activity, healthy eating and alcohol. The recommendations in several of these areas are supported by evidence extrapolated from large studies conducted in the general population and these recommendations have been graded accordingly.

3.1 DELIVERY OF LIFESTYLE INTERVENTIONS

3.1.1 WHICH LIFESTYLE INTERVENTIONS HAVE BEEN SHOWN TO WORK IN DIABETES?

- Intensive interventions which include frequent contact with health professionals, telephone contact, multiple injections and self-monitoring have led to improvements in self-management.[18]
- Education which is supplemented by additional support / follow up and behaviour modification may result in improvements in metabolic and psychosocial outcomes.[49-51]
- Computer-assisted programmes which provide education and trigger self-management have proven benefit in terms of both metabolic and psychosocial outcomes.[52,53]
- Psychological interventions which are varied and include behaviour modification, motivational interviewing, patient empowerment and activation have a positive impact on outcomes. However, the interventions vary greatly and it is not possible to state which element is of proven value.
- Interventions based on a theoretical model or knowledge base have better outcomes.

1^{++}, 1^{+}, 2^{++}

A **Patients with diabetes should be offered lifestyle interventions based on a valid theoretical framework.**

B **Education programmes, computer-assisted packages and telephone prompting should be considered as part of a multidisciplinary lifestyle-intervention programme.**

There is no evidence of benefit for interventions based in secondary care over those based in primary care. No evidence was identified which addresses long term follow up in educational interventions.

The evidence of the role health beliefs play in diabetes self management is equivocal.

Telephone or postal reminders prompting people with diabetes to attend clinics or appointments are an effective method of improving attendance.[54] 4

3.1.2 TRAINING HEALTH PROFESSIONALS TO DELIVER LIFESTYLE INTERVENTIONS

Patient satisfaction and knowledge improve when lifestyle interventions are delivered by primary care staff who have been trained to take a patient-centred approach.[55] 1^{+}

One study indicated that primary care nurses in contact with diabetes nurse educators are more knowledgeable about diabetes than nurses with no specific training in diabetes, and provide a higher standard of care.[56] 3

B **Health care professionals should receive training in patient-centred interventions in diabetes.**

3.2 SELF-MONITORING OF GLYCAEMIC CONTROL

The literature in this area is difficult to assess. Many of the studies cannot be compared as the patient groups were different and glucose monitoring was usually just one part of a multifactorial intervention programme.[57] However, a comprehensive package of care which includes glucose self-monitoring is usually effective in improving glycaemic control in type 1 diabetes.

No studies have adequately assessed the benefits of glucose monitoring on glycaemic control, or the relative benefits of blood glucose monitoring vs. urine testing. In general, urine testing is less costly than blood testing, however the preferred method of glucose monitoring varies according to type of diabetes. Some patients with type 2 diabetes prefer urine testing while patients with type 1 diabetes appear to favour blood testing.

3.3 QUALITY OF LIFE AND DEPRESSION

Quality of life issues and depression are important factors which may influence how patients are able to manage their diabetes.

3.3.1 DEPRESSION AND DIABETES

Depression is more common in people with diabetes than in the general population.[58,59] The presence of microvascular and macrovascular complications are associated with a higher prevalence of depression and lower quality of life.[60-62] Remission of depression is often associated with an improvement in glycaemic control.[58,62] | 1^+, 2^{++}, 4

Antidepressant therapy with a selective serotonin reuptake inhibitor (SSRI) is a useful treatment in depressed patients with diabetes and may improve glycaemic control,[63] however tricyclic antidepressants may adversely affect metabolic control.[64] | 1^+

Cognitive behavioural therapy (CBT) is a psychological treatment which attempts to find links between the person's feelings and the patterns of thinking which underpin their distress. CBT, psychotherapy programmes and coping skills training are useful in treating depression in patients with diabetes.[65-67] However, cognitive behavioural therapy is less effective in patients with complications.[62] | 1^{++}, 1^+, 2^{++}

The management of patients with post natal depression is considered in a forthcoming SIGN guideline.

B **Health care professionals should be aware of the effects of depression on diabetes.**

B **All people with diabetes should be screened for depression and offered appropriate therapy.**

B **SSRIs are recommended in preference to tricyclic antidepressants for treatment of depression in patients with diabetes.**

There is some evidence that negative life events are associated with poorer diabetic control.[68] | 2^+

☑ Health care professionals should be aware of the potential effects of life events on stress and self-care behaviour.

3.3.2 DIABETES CONTROL AND QUALITY OF LIFE

Severe hypoglycaemia may adversely affect quality of life in patients treated with insulin, particularly in those newly diagnosed. Improvements in blood glucose control are associated with improvements in quality of life, providing there is no increase in hypoglycaemic symptoms.[69,70] Frequency of insulin dose adjustment does not appear to affect quality of life.[17,69-71] | 1^+

B **Patients and health care professionals should make every effort to avoid severe hypoglycaemia, particularly in those who are newly diagnosed.**

3.4 SMOKING CESSATION

Smoking is an established risk factor for cardiovascular and other diseases. However, there is conflicting evidence regarding the effect of smoking on glycaemic control.

3.4.1 ASSESSMENT OF READINESS TO CHANGE SMOKING BEHAVIOUR

Standard models for measuring stages of change (pre-contemplation, contemplation, preparation, action, maintenance and relapse) have been used to assess readiness to quit smoking. There is some evidence that interventions aimed at discussing the benefits of quitting smoking may be most useful for pre-contemplators and contemplators, whereas interventions aimed at improving self-efficacy may be more useful for those preparing to quit.[72,73] 3

D **A model using stages of change may help health care professionals understand how ready an individual is to quit smoking.**

3.4.2 FIRST LINE TREATMENTS

Simple advice to stop smoking given by a physician, a nurse or a counsellor has a small but significant effect (absolute quitting rate increased by 2.5-14.7%).[74-76] Increasing the intensity of the advice is marginally more effective. Group behaviour therapy is more effective than self-help material but has not been proven to be superior to individual advice.[74,77] 1^{++}

A **Health care professionals involved in caring for patients with diabetes should advise them not to smoke.**

Nicotine replacement therapy (NRT) is effective in increasing the rate of quitting by 1.5 to 2 times.[78] All the commercially available forms of replacement (gum, patch, nasal spray, inhaler and sublingual tablets) have broadly similar efficacy. The absolute size of effect will depend on the setting. There is no evidence of the benefit of NRT in those smoking less than 15 cigarettes per day. Highly dependent smokers may benefit more from NRT and may need a higher dose. Eight weeks of patch therapy has been shown to be as effective as longer duration of therapy.[78] 1^{++}

B **Nicotine replacement therapy should be provided for smokers of more than 15 cigarettes per day who are trying to quit. Therapy in a form acceptable to the patient should be offered for up to eight weeks.**

Bupropion increases the rate of smoking cessation.[79] Combination of this with a nicotine patch is more efficacious than using a patch alone. The two studies which demonstrated these effects gave therapy for one week before quitting and for seven or eight weeks after stopping smoking.[80,81] Combination of bupropion with nicotine patch increased blood pressure in some patients. 1^{++}, 1^{+}

The above studies were not specifically of people with diabetes. The summary of product characteristics recommends a lower dose of bupropion on oral hypoglycaemic agents or insulin, as there is a greater risk of seizure.

B **Bupropion therapy (in the absence of contraindications) could be used alone or with nicotine replacement, if blood pressure is monitored.**

3.4.3 OTHER TREATMENTS

Clonidine and nortriptyline can increase rates of smoking cessation, however there are potential side effects with clonidine use.[79,82] 1^{++}

B **Other therapies which may be considered include clonidine and nortriptyline, however care should be taken to monitor for adverse effects.**

Acupuncture and silver acetate treatment are ineffective interventions in smoking cessation.[83,84] 1^{++}

B **Acupuncture or silver acetate should not be used as part of a smoking cessation strategy.**

The evidence on hypnotherapy, nurse counselling plus support, and rapid smoking aversion therapy in smoking cessation in patients with diabetes is of too poor quality to support recommendations.

3.4.4 MONITORING

Relapse to smoking remains a problem even in those patients who have successfully quit at one year. The relapse rate has been recorded as 23-40%.[85,86] 1+

B **Health care professionals should continue to monitor smoking status in all patient groups.**

3.5 EXERCISE AND PHYSICAL ACTIVITY

3.5.1 DEFINITIONS

Physical activity is defined as any skeletal muscle movement which expends energy beyond resting level (e.g. walking, gardening, stair climbing).

Exercise is a subset of physical activity which is done with the goal of enhancing or maintaining an aspect of fitness (e.g. aerobic, strength, flexibility, balance body mass index). It is often supervised (e.g. in a class), systematic and regular (e.g. jogging, swimming, attending exercise classes).

3.5.2 EFFECTS OF PHYSICAL ACTIVITY ON THE PREVENTION OF DIABETES

Regular physical activity is associated with a reduced risk of development of type 2 diabetes. This risk reduction is consistent over a range of intensity and frequency of activity, with a dose-related effect. Greater frequency of activity confers greater protection from development of type 2 diabetes and this is valid for both vigorous and moderate intensity activity. The length of time to confer the effect is greater than one year and, on current evidence, requires a minimum of four years.[87-93] 2++, 2+

The Diabetes Prevention Program (DPP) is a major study currently in progress to determine whether intensive lifestyle intervention or treatment with metformin delays or prevents the onset of diabetes. Preliminary results indicate a substantial decrease in progression from IGT to diabetes in patients who follow a programme of intensive lifestyle management.[94]

B **All people should be advised to maintain at least moderate levels of physical activity (e.g. daily walking) as a lifelong lifestyle modification.**

3.5.3 ASSESSMENT OF PHYSICAL ACTIVITY

Physical activity is a very difficult behaviour to measure since it incorporates mode of activity, duration, frequency and intensity. There is no gold standard and techniques range from heart rate monitoring to motion counters and self-reports. Self-report is the easiest format but there is often an over-reporting of minutes spent in activity. The Scottish Physical Activity Questionnaire is an example of one self-report format that has known validity and reliability for assessing moderate activity.[95] As with smoking cessation (*see section 3.4*), it is important in assessing what kind of support a patient needs for increasing or maintaining physical activity to know their stage of change. A rate of perceived exertion scale is useful for estimating exercise intensity, particularly in people with autonomic neuropathy who have reduced maximal heart rate.[96] 4

3.5.4 PHYSICAL ACTIVITY AND EXERCISE FOR PEOPLE WITH DIABETES

Various guidelines exist for physical activity and exercise in the general population. For example, for aerobic fitness a minimum of 20 minutes of continuous aerobic exercise reaching at least 50% of maximal aerobic capacity (which would equate to brisk walking for people with low fitness levels) on three days each week is recommended.[97] The Health Education Board for Scotland (www.hebs.co.uk) recommends a two-stage approach. The first stage is to encourage sedentary people to accumulate moderate physical activity for 30 minutes on most days of the week. The second stage is to encourage those who are interested, motivated and already active to engage in more vigorous activity at least three days of the week. 4

In people with type 2 diabetes physical activity or exercise should be performed at least every second or third day to maintain improvements in glycaemic control. In view of insulin adjustments etc. it may be easier for people with type 1 diabetes to perform physical activity or exercise every day.[98]

Aerobic, endurance exercise is usually recommended, however resistance training with low weights and high repetitions is also beneficial.[99] | 1+

D **Exercise and physical activity (involving aerobic and/or resistance training) should be performed on a regular basis.**

No trial-based evidence was identified which described how to promote physical activity for patients with diabetes. Expert opinion suggests using social-cognitive models and making advice person-centred and diabetes-specific.[100] | 4

D **Advice about exercise and physical activity should be individually tailored and diabetes-specific and should include implications for glucose management.**

Evidence from the non-diabetic population suggests that teaching CBT skills, tailoring advice to stage of exercise behaviour change and providing on going support (for all stages) will enhance long term adherence.[101] The most appropriate mode of activity for adherence is home based, individual, lifestyle exercise of moderate intensity (i.e. activity that is incorporated into daily life such as walking gardening or stair climbing).[102,103] Continual support appears to be required to maintain adherence, however the intensity of support required is as yet unknown.[104] | 1+, 4

C **To maximise adherence, exercise programmes should be home-based and should be accompanied by ongoing support which includes education in cognitive behaviour skills and advice tailored to the individual's stage of change.**

3.5.5 ADVICE FOR PATIENTS TAKING INSULIN OR ORAL ANTIDIABETIC DRUGS

Exercise with normal insulin dose and no additional carbohydrate significantly increases the risk of hypoglycaemia during and after exercise. If exercise can be anticipated, a reduction of the normal insulin dose (by up to 65% for vigorous exercise of up to 45 minutes) will significantly reduce the risk of hypoglycaemia and delayed hypoglycaemia.[105] | 2+

The amount of reduction in insulin dose will depend on the duration and intensity of exercise being performed, insulin and glycaemic level before exercise, and the time of day. If exercise cannot be anticipated and the insulin dose has already been taken, extra carbohydrate before exercise will reduce the risk of hypoglycaemia.

Injecting insulin into exercising areas increases its absorption and the risk of hypoglycaemia and should therefore be avoided.[105-107] | 2+

C **Individualised advice on avoiding hypoglycaemia when exercising by adjustment of carbohydrate intake, reduction of insulin dose, and choice of injection site, should be given to patients taking insulin.**

High temperatures can also increase insulin absorption. This should be taken into consideration when exercising in hot climates. A further reduction in insulin dose may be required. | 4

Patients using oral antidiabetic drugs, such as sulphonylureas, may also be at risk of hypoglycaemia during exercise.

3.5.6 DIABETIC COMPLICATIONS AND EXERCISE

There is no known association between exercise participation and development or exacerbation of diabetic complications, however exercise during insulin deficiency can cause hyperglycaemia.[105] | 4

Research demonstrates that high intensity exercise may transiently increase the albumin excretion rate in people with or without diabetes. No evidence of more rapid progression of nephropathy or retinopathy was identified in people with diabetes who exercise vigorously.[108,109] However, in theory, haemodynamic changes which accompany high intensity exercise could have an adverse effect on microvascular disease. | 2+

A joint position statement from the American Diabetes Association and American College of Sports Medicine [97,98] recommends that patients with diabetes planning moderate to high intensity exercise should undergo graded exercise testing if one or more of the following criteria apply:

- age >35 yrs
- type 2 diabetes >10 years duration
- type 1 diabetes >15 years duration
- presence of any additional risk factor for cardiovascular disease (CVD)
- presence of microvascular disease (retinopathy or nephropathy, including microalbuminuria)
- peripheral vascular disease
- autonomic neuropathy.

4

Graded exercise testing is not standard clinical practice in the UK, however, it can provide useful information if time and resources allow.

There is higher risk of myocardial infarction (MI) after heavy exertion in sedentary compared with non-sedentary people with type 1 diabetes.[110] 2+

D **Patients with existing complications of diabetes should seek medical review before embarking on exercise programmes.**

D **A gradual introduction and initial low intensity of physical activity should be recommended for sedentary people with diabetes.**

3.6 HEALTHY EATING

3.6.1 RECOMMENDED DIET FOR PEOPLE WITH DIABETES

Healthy eating is of fundamental importance as part of diabetes health care behaviour and has beneficial effects on weight, metabolic control and general well-being. In particular, weight control in overweight subjects with diabetes is associated with improved glycaemic control.[111,112] Salt restriction in the general population is discussed in the SIGN guideline on lipids and the primary prevention of coronary heart disease (SIGN 40).[113] Dietary recommendations, including dietary constituents for healthy eating and weight control in patients with diabetes, are summarised elsewhere.[114,115] 1+, 4

3.6.2 DIETARY INTERVENTIONS TO PREVENT THE ONSET OF DIABETES

There is conflicting evidence for the role of specific dietary intervention programmes. Studies either show a beneficial effect or no effect, but there is no evidence of a harmful effect. Most recently, one large trial from Finland demonstrated a short term reduction in the development of type 2 diabetes in high risk subjects (overweight and impaired glucose tolerance) by encouraging lifestyle change, including diet and exercise advice. It is not possible to determine which aspects of the programme were successful.[116] However, other studies have demonstrated that if people who are overweight lose weight, by whatever method, their risk of developing diabetes is reduced.[89,112,117-119] 1+

B **Overweight individuals and those at high risk of developing diabetes should be encouraged to reduce their risk by lifestyle changes.**

3.6.3 ASSESSMENT OF DIET IN CLINICAL PRACTICE

There are few studies which have examined the validity of dietary assessments in clinical practice, particularly in patients with diabetes. Self-report questionnaires have been developed and are currently being validated.[120-125] The most accurate form of dietary assessment is the seven day weighed food record, although this is impractical in the clinical setting. Assessment of diet over shorter periods is less accurate.[126] 4

3.6.4 ASSESSING READINESS TO CHANGE DIETARY BEHAVIOUR

The stages of change (transtheoretical) model is valid when assessing dietary behaviour.[127] Questionnaires to assess the stage of change of a patient are easily administered in clinical practice.[128,129] 3

D **Before giving dietary advice to patients with diabetes, assessment of readiness to change diet behaviour should be undertaken.**

3.6.5 ENCOURAGING DIETARY CHANGE IN CLINICAL PRACTICE

The use of a behavioural approach to dietary interventions in patients with diabetes shows clinically significant benefit in terms of weight loss, HbA_{1c}, lipids, and self-care behaviour for up to two years after the initial intervention.[130-136] However, it is not always possible to identify if the benefit is wholly attributable to the intervention, or is dependent on how or where the care is delivered. 1^+

Intensive therapy or contact in patients with diabetes shows clinically beneficial effects on weight and glycaemic control during the period of intervention. More education and contact appears to improve outcomes.[137-141] Pre-packaged meal programmes show significant clinical benefit in terms of weight, blood pressure, glycaemic control and lipids during the study period but are impractical outside the trial setting.[142-145] 1^+

B **Clinical interventions aimed at dietary change are more likely to be successful if a psychological approach based on a theoretical model is included.**

3.7 ALCOHOL

In people with type 1 diabetes, drinking 2-3 glasses of wine at one time in the rested state has no significant effect on blood glucose up to 10 hours after consumption.[146-148] 1^+

In people with type 2 diabetes, drinking 2-3 glasses of wine or an equivalent quantity of beer may result in a non-significant decrease in blood glucose, but no increased risk of hypoglycaemia.[149-151] However, if patients with type 2 diabetes exercise after drinking alcohol blood glucose may be lowered by up to 27% from baseline, but in the laboratory situation there was no increased risk of developing hypoglycaemia.[150] 1^+

All patients with diabetes should be aware of the high calorific value of alcohol and the implications of excess consumption on body weight.

B* **Patients with diabetes should be advised that they may drink up to 3 units of alcohol with a minimal effect on blood glucose. Patients should be advised that if exercise and consumption of alcohol are combined there may be a greater lowering of blood glucose.**

☑ Excess alcohol consumption is associated with a worsening in general health and can lead to weight gain, reduced fertility and memory loss. As in the general population, alcohol consumption should be limited to 3-4 units per day in men and 2-3 units per day in women.

** The grade of recommendation has been adjusted due to setting and sample sizes of trials.*

4 Management of diabetic cardiovascular disease

4.1 EPIDEMIOLOGY

Morbidity and mortality from cardiovascular disease (CVD) are two to five times higher in patients with diabetes compared with non-diabetics.[152-158] Women with diabetes have been shown to have a higher relative risk of death from cardiovascular disease than men, although the absolute risk is lower.[156,159,160] Diabetes is associated with excess mortality, even in areas with high background death rates from cardiovascular disease. This excess mortality is evident in all age groups, most pronounced in young people with type 1 diabetes, and exacerbated by socio-economic deprivation. The life expectancy of both men and women diagnosed as having type 2 diabetes at age 40 is reduced by eight years relative to people without diabetes.[161,162] There is an increased prevalence of cardiovascular disease in South Asian individuals with diabetes[156,157] although the United Kingdom Prospective Diabetes Study (UKPDS) reported no increase in the incidence of acute myocardial infarction compared to caucasian subjects.[163]

4.2 CARDIOVASCULAR RISK FACTORS

Cigarette smoking

The prevalence of smoking is significantly higher among patients with diabetes than the non-diabetic population (33% vs 27%).[164]

Smoking is an independent risk factor in people with diabetes[165-167] and the excess risk attributable to smoking is more than additive.[168] | 2^{++}

Dyslipidaemia

Dyslipidaemia is commonly present in patients with type 2 diabetes.[169] An increased concentration of low density lipoprotein (LDL) cholesterol or total cholesterol is an independent risk factor for cardiovascular morbidity and mortality.[165,167] Each 1 mmol/l reduction of LDL cholesterol represents a 36% reduction in risk of CVD disease. | 2^{++}

Triglycerides are an independent marker of increased risk of cardiovascular disease in type 2 diabetes.[170] The ongoing Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study (n = 8,000) is addressing whether lowering serum triglyceride concentrations reduces CVD events in patients with diabetes with and without coronary heart disease. | 2^{+}

Hypertension

Hypertension is positively related to risk of CVD death, with a progressive increase in risk with rising systolic pressures.[165-167] Each 10 mm Hg reduction in systolic pressure is associated with a 15% (95% CI 12-18%) reduction in the risk of CVD death over 10 years.[171] | 2^{++}

Hyperglycaemia

Increasing glycaemia (measured as HbA_{1c}) results in increased risk of CVD morbidity and mortality.[165] Each 1% reduction in HbA_{1c} is associated with a 21% (95% CI 15-27%) reduction in the risk of diabetes-related death and specifically a 14% reduction for myocardial infarction (MI) over 10 years. No lower threshold can be demonstrated.[172] | 2^{++}

Other potential risk factors

No studies identifying obesity as an independent risk factor in established diabetes were identified. In addition to its role in identifying patients at risk of diabetic nephropathy (*see section 5*), microalbuminuria is an independent marker associated with a doubling in cardiovascular risk.[173] There is insufficient evidence to determine whether reducing albumin excretion rate specifically reduces cardiovascular morbidity or mortality.

4.3 PRIMARY PREVENTION OF CORONARY HEART DISEASE

4.3.1 LIFESTYLE MODIFICATION

Lifestyle modification as discussed in section 3 is recommended to reduce cardiovascular risk factors.

4.3.2 PHARMACOLOGICAL THERAPY

There have been many large randomised clinical trials that have evaluated pharmacological treatments in reducing cardiovascular disease. Until recently, most trials have not randomised a large proportion of people with type 1 and type 2 diabetes; whereas in clinical practice, cardiovascular disease is the principal cause of morbidity and mortality in people with diabetes.

Glucose lowering

In a substudy of the UKPDS, 1,704 overweight patients (>120% ideal body weight) who had fasting plasma glucose between 6.1 and 15.0 mmol/l were randomised to conventional (diet) therapy (24%), or to intensive treatment with either chlorpropamide (16%), glibenclamide (16%), insulin (24%), or metformin (20%). The patients assigned metformin, compared with the conventional group, had risk reductions of 32% (95% CI 13-47%, p = 0.002) for any diabetes-related endpoint, 42% for diabetes-related death (95% CI 9-63%, p = 0.017), and 36% for all-cause mortality (95% CI 9-55%, p = 0.011). Among patients allocated intensive blood glucose control, metformin showed a greater effect than chlorpropamide, glibenclamide, or insulin for any diabetes-related endpoint, all-cause mortality, and stroke.[174] | 1+

A **Metformin should be considered as the first-line oral hypoglycaemic agent in overweight patients with diabetes**.

Antihypertensive therapy

Blood pressure (BP) lowering in people with diabetes reduces the risk of macrovascular and microvascular disease.[171,172,175] | 1+

A **Hypertension in people with diabetes should be treated aggressively with lifestyle modification and drug therapy.**

The lowering of blood pressure to 80 mm Hg diastolic is of benefit in people with diabetes. In the Hypertension Optimal Treatment (HOT) study, the lowest incidence of major cardiovascular events in all patients occurred at a mean achieved diastolic blood pressure of 82.6 mm Hg and further reduction below this blood pressure was safe in patients with diabetes. There was a 51% reduction in major cardiovascular events in the BP target group ≤80 mm Hg compared with target group ≤90 mm Hg (p = 0.005).[176] | 1++

A **Target diastolic blood pressure in people with diabetes is ≤80 mm Hg.**

In the HOT study, although diastolic BP was accurately measured, systolic BP was consistently underestimated. The reported achieved systolic BP of 139.7 mm Hg in patients with a diastolic target of ≤80 mm Hg is likely to have been closer to 146 mm Hg.[177] In the UKPDS, the achieved systolic BP of 144 mm Hg in patients allocated to 'tight control' was observed when aiming for a systolic BP <150 mm Hg. In an epidemiological analysis, lowest risk was observed in those with a systolic BP <120 mm Hg.[171]

The British Hypertension Society recommends a target systolic BP of 140 mm Hg in non-diabetic and diabetic subjects. | 4

D **Target systolic blood pressure in people with diabetes is <140 mm Hg.**

Thiazides, β-blockers, angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers are all effective in lowering blood pressure and reducing the risk of cardiovascular events.[178-179] ACE inhibitors should be considered as first line therapy in patients with microalbuminuria due to their additional benefit on renal function (*see section 5.5.2*). | 1++

Angiotensin II receptor blockers are useful alternative antihypertensive agents in patients with ACE inhibitor-induced cough or rash. They have similar renal benefits in patients with microalbuminuria,[180] but have not yet been shown to decrease cardiovascular events. 1++

Aspirin therapy

There remains uncertainty about the role of aspirin in primary prevention. In the HOT study low dose aspirin further reduced cardiovascular risk in well-controlled hypertensive patients with diabetes,[176] but its use must be balanced against the risk of bleeding. 1+

This balance of benefit over risk increases with the absolute risk of MI, which can be estimated from, for example, the Joint British Guidelines.[181] (*See the SIGN guideline on lipids and the primary prevention of coronary heart disease (SIGN 40)*[113]). The use of aspirin and other antiplatelet agents in primary prophylaxis of myocardial infarction in high risk patients is discussed in the SIGN guideline on antithrombotic therapy.[182]

B **Aspirin (75 mg) should be considered for all patients who have diabetes and well-controlled hypertension whose risk of a coronary event is estimated to be >20% over 10 years.**

Lipid lowering

Treatment with lipid lowering drugs reduces coronary heart disease events but not all cause mortality in people with no known cardiovascular disease. Lipid lowering for the primary prevention of coronary heart disease is discussed in SIGN 40,[113] which includes the following recommendations: 4

D **As for non-diabetics, lipid lowering drug therapy should be considered for primary prevention in patients with type 2 diabetes without evidence of nephropathy when the 10 year risk of a major coronary event is ≥30% using the Joint British Chart.**

D **Current assessment methods may underestimate risk in patients with type 1 diabetes and in patients with type 2 diabetes and nephropathy. Lipid lowering drug therapy should be considered at a lower risk threshold in these individuals.**

4.4 MANAGEMENT OF THE PATIENT WITH DIABETES AND NEW OR ESTABLISHED VASCULAR DISEASE

Myocardial infarction is a common cause of death in people with diabetes. The principles of management are as for patients without diabetes (*see the SIGN guideline on secondary prevention of coronary heart disease following myocardial infarction* (*SIGN 41)*[183]). However, the case fatality from myocardial infarction is double that of the non-diabetic population.[184] Patients with diabetes more often present with a painless or 'silent' MI, which leads to a delay in admission to hospital.

4.4.1 USE OF INSULIN

A prospective randomised controlled study of intensive insulin treatment on long term survival after MI in patients with diabetes showed a reduction in mortality at one year. Insulin-glucose-potassium infusion for at least 24 hours, followed by four times daily insulin treatment for at least three months, was shown to improve long term survival, with an absolute reduction in mortality of 11%.[185] 1++

It is not clear which element of treatment led to this improvement in survival and a further study is due for completion by 2003 to determine whether the reduction in mortality is caused by the infusion, the subcutaneous insulin treatment, or both.

B **Patients with diabetes should be considered for intensive insulin treatment following acute MI.**

4.4.2 THROMBOLYSIS

Thrombolytic therapy has been shown to reduce mortality after acute MI in subjects with diabetes by up to 42%, with no increase in risk of bleeding or stroke. It should not be withheld due to concern about retinal haemorrhage in patients with retinopathy, and the indications and contraindications for thrombolysis in patients with diabetes are the same as in non-diabetic subjects.[186] 1+

A **Patients with diabetes should be given thrombolytic therapy following myocardial infarction.**

4.4.3 PRIMARY CORONARY ANGIOPLASTY FOR ACUTE MI

Subgroup analysis has shown that primary angioplasty is similarly successful in patients with and without diabetes, and may be more effective than thrombolytic therapy in subjects with diabetes either with or without acute myocardial infarction.[187,188] 2+

C **Patients with diabetes should be considered for primary angioplasty for acute myocardial infarction.**

4.4.4 β-BLOCKERS

Diabetes is not a contraindication to the use of β-blockers, which reduce mortality, sudden cardiac death and re-infarction when given after acute myocardial infarction.[189] 1++

A **β-blocker therapy should be considered for all patients following myocardial infarction.**

4.4.5 ANTIPLATELET THERAPY

Meta-analysis of platelet inhibitor therapy has demonstrated a 31% reduction in non-fatal re-infarction, a 42% reduction in non-fatal stroke, and a 13% reduction in cardiovascular mortality.[190] 1++

A **Aspirin (75 mg per day) should be given routinely and continued long term in patients with diabetes and coronary heart disease.**

Substudy analysis of a large RCT has demonstrated that addition of clopidogrel to aspirin over 3-12 months may reduce the risk of fatal or non-fatal myocardial infarction or stroke by 20% in patients with a past history of coronary heart disease presenting with acute coronary syndromes (i.e without electrocardiographic ST elevation). This risk reduction is associated with an additional risk of bleeding.[191] 1++

B* **Addition of clopidogrel 75 mg daily to usual aspirin therapy should be considered for patients with diabetes and a past history of coronary heart disease presenting with acute coronary syndromes.**

4.4.6 ACE INHIBITORS

A meta-analysis of nearly 100,000 patients receiving therapy with an ACE inhibitor within 36 hours of acute MI and continued for at least four weeks, confirmed that ACE inhibitors reduce mortality. Most of the benefits appeared to occur during the first few days, when mortality was highest; and patients at higher risk appeared to benefit to a greater absolute extent.[192]

Three large trials (the AIRE, SAVE and TRACE studies) have shown consistent reductions in mortality when ACE inhibitor therapy is given to people after acute MI with clinical evidence of heart failure or a reduced ejection fraction.[193-195] 1++, 1+

In the large SOLVD study, the absolute risk reduction for mortality in patients with diabetes with chronic heart failure was 4.5% over a mean follow-up of 4.5 years. The much smaller CONSENSUS-1 study showed more dramatic reductions in mortality.[196,197]

**The grade of recommendation has been adjusted due to derivation from a substudy analysis.*

The HOPE study, a large, multi-national RCT, showed benefit of ramipril in 3,577 people with diabetes. The combined primary outcome was myocardial infarction, stroke, or cardiovascular death. Ramipril lowered the risk of the combined primary outcome by 25%, myocardial infarction by 22%, stroke by 33%, cardiovascular death by 37%, and total mortality by 24% After adjustment for the changes in systolic (2.4 mm Hg) and diastolic (1.0 mm Hg) blood pressures, ramipril still lowered the risk of the combined primary outcome by 25% (95% CI 12-36%, p = 0.0004).[198] 1++, 1+

	ACE inhibitor therapy should be given to patients with diabetes who fall into any of the following categories:
B	▪ **following MI with or without left ventricular dysfunction**
B	▪ **heart failure due to left ventricular systolic dysfunction**
A	▪ **aged >55 years and who smoke, have total cholesterol >5.2 mmol/l, HDL cholesterol ≤0.9 mmol/l, microalbuminuria or hypertension.**

A	**In post MI patients with left ventricular dysfunction, ACE inhibitor therapy should be considered within 48 hours of the onset of symptoms.**

☑	In the presence of significant bilateral renal artery stenosis, ACE inhibitor therapy is associated with acute renal failure and should not be used.

4.4.7 LIPID LOWERING

The most common type of dyslipidaemia in type 2 diabetes is the combination of elevated triglycerides, low high density lipoprotein (HDL) and small, dense LDL.[199] The current evidence of benefit with lipid lowering drugs is derived from sub-group analysis of studies that were selected without primary reference to diabetes.

The Scandinavian Simvastatin Study (4S) included 204 patients with diabetes out of a total of 4,444 subjects. It demonstrated that cholesterol-lowering therapy was highly effective with significant reductions in cardiovascular deaths, cardiovascular events, and the need for revascularisation procedures. These effects appeared more marked in patients with diabetes than those without diabetes (risk reduction 55% vs 32%). The threshold for initiating treatment with a statin was total cholesterol >5.0 mmol/l and/or LDL cholesterol >3.0 mmol/l on diet.[200] The Cholesterol and Recurrent Events study (CARE), like 4S, demonstrated a statistically significant reduction in coronary events in patients with diabetes treated with pravastatin although the magnitude of the effect in this North American study was less than that in 4S.[201,202] The Long Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study showed a trend to reduction in recurrent coronary events, but the numbers (782 patients with diabetes) were insufficient to demonstrate statistical significance.[203] 1+

B	**If total cholesterol is >5.0 mmol/l, statin therapy to reduce cholesterol should be initiated and titrated as necessary to reduce total cholesterol to <5.0 mmol/l.**

The effectiveness of gemfibrozil in the secondary prevention of coronary events in men with coronary disease and 'low HDL dyslipidaemia' has been examined in the VA-HIT study, which showed a significant reduction in coronary events in men with diabetes under the age of 74 over a mean follow up period of 5.1 years.[204] 1+

B	**In patients with established CVD who are not receiving statin therapy and whose total cholesterol is <5.0 mmol/l and HDL cholesterol <1.0 mmol/l, gemfibrozil should be considered.**

4.4.8 CORONARY REVASCULARISATION

Patients with diabetes are at increased risk of complications during revascularisation procedures. There is an increased risk of mortality following both coronary bypass surgery and angioplasty; and there is a substantially increased risk of re-stenosis following angioplasty in diabetic patients, partly ameliorated by the use of coronary stents. Much of this increased risk is due to confounding associations, e.g. female sex, diffuse coronary disease, impaired left ventricular function and renal impairment, rather than the diabetic state itself. Indications for coronary angiography in patients with diabetes with symptomatic coronary disease are similar to those in non-diabetics, recognising the increased risk associated with revascularisation procedures.

Recommendations on revascularisation in the general population are given in the SIGN guideline on coronary revascularisation in the management of stable angina pectoris (SIGN 32).[205]

The BARI trial[206] suggested that amongst patients with diabetes coronary atery bypass grafting (CABG) using internal mammary arteries was associated with a better survival rate than percutaneous transluminal coronary angioplasty (PTCA) although this trial was conducted before the advent of the routine use of stenting. However, the more recent EAST trial showed similar conclusions.[207] The American College of Cardiology / American Heart Association Task Force recommend CABG over PTCA in patients with multivessel disease.[208] 1+, 4

B **For patients with diabetes and multivessel disease, CABG with use of the internal mammary arteries is preferred over PTCA.**

Stenting improves the outcome after angioplasty.[209] Platelet glycoprotein IIb/IIIa receptor antagonists (e.g. abciximab) also reduce mortality after angioplasty with or without stenting in patients with diabetes.[210-213] 1++

A **Patients with diabetes undergoing angioplasty should be treated with stents where feasible, and receive adjunctive therapy with a platelet glycoprotein IIb/IIIa receptor antagonist.**

4.5 MANAGEMENT OF ACUTE STROKE

The incidence of stroke in patients with diabetes is high, and the mortality following stroke is increased compared to non-diabetic patients. The clinical presentation is similar to that in non-diabetic subjects.[214] There is little evidence specific to people with diabetes. Management of stroke is similar to that in non-diabetic subjects. Rehydration and intravenous insulin may also be required. 4

4.6 PERIPHERAL ARTERIAL DISEASE

The most common complications of peripheral arterial disease are lower limb ischaemia, gangrene and amputation (*see section 7*).

5 Management of diabetic nephropathy

This section of the guideline focuses on the prevention, detection and treatment of diabetic nephropathy, and the management of cardiovascular risk in those with diabetic nephropathy, rather than renal disease(s) in those with diabetes. The guideline excludes the management of end-stage renal disease and renal replacement therapy.

5.1 DEFINITIONS

Microalbuminuria is defined by a rise in urinary albumin loss to between 30 and 300 mg/day. To avoid a timed urine collection, a urinary albumin:creatinine ratio (ACR) >2.5 mg/mmol in men and >3.5 mg/mmol in women or a urinary albumin concentration >20 mg/l are adequate.[215] This is the earliest sign of diabetic nephropathy and predicts increased total mortality, cardiovascular mortality and morbidity, and end-stage renal failure.

Diabetic nephropathy is defined by a raised urinary albumin excretion of >300 mg/day (indicating clinical proteinuria) in a patient with or without a raised serum creatinine level and with co-existing diabetic retinopathy. An ACR > 30mg/mmol in a spot urine sample indicates diabetic nephropathy. This represents a more severe and established form of renal disease and is more strongly predictive of total mortality, cardiovascular mortality and morbidity, and end-stage renal failure than microalbuminuria.

5.2 PREVALENCE AND DISEASE PROGRESSION

5.2.1 TYPE 1 DIABETES

The cumulative incidence of microalbuminuria in patients with type 1 diabetes at 30 years disease duration is approximately 40%.[216-218] For microalbuminuric patients the relative risk of developing proteinuria is 9.3 compared to normoalbuminuric patients.[219] Approximately 20% of type 1 patients develop proteinuria after a disease duration of 25 years.[216-218]

The majority of microalbuminuric type 1 patients will progress to develop proteinuria, although some may revert to normoalbuminuria.[220, 221] With aggressive antihypertensive therapy proteinuric type 1 patients lose glomerular filtration rate (GFR) at approximately 4 ml/min/year.[222] When proteinuria and hypertension are present the standardised mortality ratio is increased 11-fold in men and 18-fold in women.[223]

5.2.2 TYPE 2 DIABETES

The cumulative incidence of microalbuminuria in patients with type 2 diabetes at 10 years disease duration is approximately 20-25%.[224] 20% of microalbuminuric type 2 patients who survive for 10 years develop proteinuria.[225] The prevalence of proteinuria in patients with type 2 diabetes is approximately 15%.[224]

Treated proteinuric, hypertensive type 2 patients lose glomerular function at a rate of approximately 8 ml/min/year.[226]

Patients with microalbuminuria have a two to fourfold increase in cardiovascular morbidity and mortality.[227] The 4-year mortality of microalbuminuric type 2 patients is 32% and 50% of proteinuric type 2 patients have died within 4 years.[228,229] When proteinuria and hypertension are present the standardised mortality ratio is increased fivefold in men and eightfold in women with type 2 diabetes.[223]

5.3 SCREENING

Measurements of urinary albumin loss and serum creatinine are the best screening tests for diabetic nephropathy.[230] Screening in young people is considered in section 2.5.2. | 3

D **All patients with diabetes should have their urinary albumin concentration and serum creatinine measured at diagnosis and at regular intervals, usually annually.**

The daily variability in urinary albumin loss can be 40%. A first morning urine sample best reflects a timed collection and provides an adequate assessment of urinary albumin loss. A normal value in a random sample confirms normoalbuminuria.[230] | 3

Measurement of urinary albumin:creatinine ratio or urinary albumin concentration is usually measured using laboratory facilities. Commercial near-patient tests for measurement of low-level albuminuria (microalbuminuria) have adequate levels of sensitivity (>80%) and specificity (>90%).[224] | 4

D **Urinary albumin concentration should be measured using a first morning urine sample and the urinary albumin:creatinine ratio should be measured by a laboratory method or a near-patient test specific for albumin at low concentration.**

D **An abnormal result should be confirmed by a further sample without delay.**

5.4 PREVENTION OF DIABETIC NEPHROPATHY

Risk factors for the development of diabetic nephropathy are:

- hyperglycaemia
- raised blood pressure
- baseline urinary albumin excretion
- increasing age
- duration of diabetes
- presence of retinopathy
- smoking
- genetic factors
- raised cholesterol and triglyceride levels
- male sex
- serum homocysteine levels.

In the DCCT study, a reduction in mean HbA_{1c} from 9.0% to 7.0% was associated with a 39% reduction in the occurrence of microalbuminuria and a 54% reduction in the occurrence of proteinuria over 6.5 years in patients with type 1 diabetes.[18] In UKPDS a reduction in mean HbA_{1c} from 7.9% to 7.0% was associated with an absolute risk reduction of developing microalbuminuria of 11%, proteinuria by 3.5% and a twofold increase in serum creatinine by 2.5% over 12 years in patients with type 2 diabetes.[231] | 1^{++}

A **Good glycaemic control (HbA_{1c} around 7%) should be maintained in all patients with diabetes to reduce the risk of developing diabetic nephropathy.**

The UKPDS also showed that a reduction in blood pressure from 154/87 to 144/82 mm Hg was associated with an absolute risk reduction for developing microalbuminuria of 8% over 6 years in patients with type 2 diabetes.[232] In the HOPE study, ACE inhibitor therapy for 4.5 years in type 2 patients was associated with an absolute risk reduction of developing proteinuria of 2%.[198] | 1^{++}

A **Tight blood pressure control (<140/80 mm Hg) in patients with type 2 diabetes should be maintained to reduce the risk of developing diabetic nephropathy.**

5.5 TREATMENT OF DIABETIC NEPHROPATHY

5.5.1 BLOOD PRESSURE CONTROL

Tight blood pressure control to <140/80 mm Hg minimises the progressive loss of renal function.[198,222,232] 1+

A **Blood pressure should be maintained <140/80 mm Hg in all patients with diabetes.**

In microalbuminuric type 1 patients, mean achieved blood pressure levels on treatment with ACE inhibitor therapy of 122/73 mm Hg and 122/79 mm Hg was associated with a 30% and 18% reduction in AER at 30 and 24 months, respectively.[233, 234] In patients with type 1 diabetes and proteinuria (established diabetic nephropathy), average blood pressure levels of 130/80 mm Hg were associated with renal benefit in the context of ACE inhibitor therapy.[235] 1+

☑ The majority of patients with diabetes will require more than one antihypertensive agent in order to achieve target blood pressure levels.

5.5.2 ACE INHIBITOR THERAPY

ACE inhibitors are more effective than other agents in reducing urinary albumin loss.[236] In type 1 patients, ACE inhibitor therapy for three years was associated with a 50% reduction in a combined end-point of death, dialysis and transplantation that was independent of blood pressure.[235] Meta-analysis has demonstrated an additional benefit on glomerular filtration rate independent of blood pressure change.[236] 1++

Treatment with an ACE inhibitors for 4.5 years in type 2 patients with microalbuminuria has been shown to reduce cardiovascular events by 25% in both those with normal serum creatinine levels and in those with mild renal insufficiency.[198,237] Most published studies have used ACE inhibitors at the higher end of their therapeutic dose ranges.[198,233-236] 1+

A **Patients with microalbuminuria or proteinuria should be commenced on an ACE inhibitor.**

☑ In the presence of significant bilateral renal artery stenosis ACE inhibitor therapy is associated with acute renal failure and should not be used.

5.5.3 ANGIOTENSIN II ANTAGONISTS

Several studies have shown the benefit of angiotensin II antagonists. In one study, 5% of microalbuminuric type 2 diabetic patients developed diabetic nephropathy when treated with an angiotensin II antagonist compared to 15% in a control group over two years.[238] This effect was independent of blood pressure reduction. At the stage of diabetic nephropathy with a reduced glomerular filtration rate, 17% of type 2 patients treated with an angiotensin II antagonist doubled their serum creatinine level over 2.6 years against 25% in a comparator group.[239] In a similar study 22% of type 2 patients treated with an angiotensin II antagonist doubled their serum creatinine level over 3.4 years against 26% in a comparator group.[240] In both of these studies the renal effect was independent of blood pressure reduction. No effect of angiotensin II antagonist therapy on mortality was seen. 1+

A **Patients with microalbuminuria or proteinuria should be considered for angiotensin II antagonist therapy.**

5.5.4 GLYCAEMIC CONTROL

The evidence for good glycaemic control in the treatment of microalbuminuria in patients with type 1 diabetes suggests no clear benefit.[221] In a small study of 52 type 2 patients with microalbuminuria, two years of intensive glucose control (HbA_{1c} 7.1% vs 9.1% in the standard control group) resulted in a stabilisation of urinary albumin excretion whereas albumin excretion rates tripled in the standard control group. However creatinine clearance rates fell in both intensive and standard control groups by 17% and 12% respectively.[241] 1+

5.5.5 DIETARY PROTEIN

Reduction of dietary protein intake to 0.6-0.8 g/kg/day reduces the rate of GFR loss in patients with type 1 diabetes who have proteinuria and impaired renal function.[242] One meta-analysis suggested that the effects of a low protein diet on the decline in the glomerular filtration rate may be greater in patients with diabetes than in those with non-diabetic causes of renal failure.[243] The effect of a reduction of dietary protein on renal function in patients with type 2 diabetes is unclear. 1++

A **Patients with type 1 diabetes, proteinuria and a reduced GFR should reduce dietary protein intake to 0.6-0.8 g/kg/day.**

☑ Patients commenced on a reduced dietary protein intake should be frequently and carefully monitored by a Registered Dietitian to ensure an adequate nutritional state.

5.5.6 REFERRAL

No evidence exists to advise on the correct time for referral to a renal clinic, however most renal physicians would prefer patients to be referred earlier rather than later.

☑ Patients should be referred to a renal clinic if serum creatinine exceeds 150 µmol/l.

There is no direct comparative data to demonstrate the effectiveness of combined diabetes/renal clinics over conventional care in the management of patients with diabetic nephropathy.

5.5.7 MANAGEMENT OF CARDIOVASCULAR RISK FACTORS

All stages of diabetic nephropathy are independent risk factors for cardiovascular disease.

☑ Patients with diabetic nephropathy should be medically managed as patients with established coronary disease (i.e. β-blockers, ACE inhibitor therapy, antiplatelet therapy and lipid lowering therapy).

6 Prevention of visual impairment

Blindness is one of the most feared complications of diabetes with an incidence of 50-65 per 100,000 diabetic population per year in Europe.[245-247] However, with good care, visual impairment due to diabetes can be avoided for the vast majority of patients.

6.1 RISK IDENTIFICATION AND PREVENTION

6.1.1 RISK FACTORS FOR DIABETIC RETINAL DISEASE

The following risk factors have been shown to determine the development and progression of diabetic retinal disease:

- poor glycaemic control[18,248,249]
- raised blood pressure[232]
- increasing number of microaneurysms[250,251]
- duration of diabetes[252,253]
- microalbuminuria and proteinuria[254,255]
- raised triglycerides and lowered haematocrit[256]
- pregnancy.[257]

1^{++}, 2^{+}

The evidence with regard to smoking as a risk factor for diabetic retinal disease is conflicting. The available evidence suggests that smoking may be a risk factor for retinopathy in type1 diabetes;[258,259] however, in type 2 diabetes, the evidence is controversial, and smoking may protect against the progression of retinopathy in certain patients.[260,261] Smoking is an independent risk factor for cardiovascular disease in all patients with diabetes and should therefore be discouraged *(see sections 3.4 and 4.2)*.

B **Patients with multiple risk factors should be considered at high risk of developing diabetic retinal disease.**

See section 8 for specific guidance on assessment and referral during pregnancy.

Diabetic retinal disease is the commonest cause of visual impairment in type 1 diabetes, but not in type 2 diabetes.[262] Patients with diabetes have approximately a twofold increased risk of cataract[263,264] and the risk is increased with poor glycaemic control.[265] One study has indicated that intensive glycaemic control reduced the incidence of cataract extraction in type 2 diabetes.[172]

2^{++}

6.1.2 RISK FACTOR MODIFICATION

The evidence that modifying risk factors has a beneficial outcome in diabetic retinal disease exists for only some of the risk factors identified above.

Tight control of blood glucose reduces the risk of onset and progression of diabetic eye disease in type 1 and 2 diabetes.[231,248,266]

1^{++}

Reducing HbA_{1c} by 1.5% and, if possible, to 7% in type 1 and 2 diabetes [231,248] and reducing blood pressure to 144/82 mm Hg in type 2 diabetes reduces the incidence and progression of sight-threatening diabetic eye disease [232] and this is likely also to be the case for type 1 diabetes.

Reducing blood pressure and HbA_{1c} below these targets is likely to reduce the risk of eye disease further.[171,172] Microvascular endpoints (including retinopathy) are decreased by 37% with each 1% reduction in HbA_{1c}, and by 13% for each 10 mm Hg reduction in systolic blood pressure[172,174] indicating that any improvement in these parameters is beneficial.

2^{++}

A **Good glycaemic control (HbA_{1c} ideally around 7%) and blood pressure control (< 140/80 mm Hg) should be maintained to prevent onset and progression of diabetic eye disease.**

Rapid improvement of glycaemic control can result in short term worsening of diabetic retinal disease although the long term outcomes remain beneficial.[248] | 2++

B **Sight-threatening retinal disease, if present, should be stabilised before rapid clinical improvements in glycaemic control are achieved.**

There is an absence of good evidence for any additional benefit of ACE inhibitors in diabetic eye disease. One recent multicentered RCT which addressed this issue was methodologically flawed,[267] however there are a number of ongoing trials involving ACE inhibitor therapy.

6.2 SCREENING

6.2.1 WHO SHOULD BE SCREENED?

Up to 39% of patients with type 2 diabetes have retinopathy at diagnosis, with 4-8% being sight-threatening.[231,268] | 1++

Screening for diabetic retinal disease is effective at detecting unrecognised sight-threatening retinopathy.[269,270] | 2++, 4

In type 1 diabetes, pre-proliferative retinopathy has been identified 3.5 years after diagnosis in post-puberty patients[271] and within two months of onset of puberty. | 2+

For patients with no retinopathy at baseline, the chance of developing sight-threatening retinopathy within two years is less than 1% in both type 1 and type 2 diabetes on preliminary data.[272,273] Patients with existing diabetic retinal disease may require more frequent retinal examination. | 2++

B **Systematic annual screening for diabetic retinal disease should be provided for all people with diabetes.**

A **Patients with type 2 diabetes should be screened from diagnosis.**

C **Patients with type 1 diabetes should be screened from age 12 years. If onset of type 1 diabetes is post-puberty, screening should start three years after diagnosis.**

6.2.2 HOW SHOULD SCREENING BE PERFORMED?

Diabetes UK propose that an effective system of screening should achieve a sensitivity of 80% and specificity of 95% with a technical failure rate of less than 5%.[269,274] Visual acuity measurements help in interpretation of maculopathy.[275] | 4

Retinal photography can frequently achieve a sensitivity of 80% and is a more effective screening method than direct ophthalmoscopy, which only rarely achieves 80% sensitivity even when carried out by properly trained operators.[270] | 2++

Between 3% and 14% of retinal photographs are ungradeable,[269,276] although this rate may be improved by digital imaging. Slit lamp biomicroscopes with dilated indirect ophthalmoscopy used by properly trained individuals can achieve sensitivities similar to,[270] or greater than,[277] retinal photography, with a lower technical failure rate. However, slit lamp biomicroscopy has only limited validation as a screening tool.[278] | 2++

Patients prefer screening to be performed at a site convenient to them.[279,280] | 4

C **Retinal photography or slit lamp biomicroscopy used by trained individuals should be used in a programme of systematic screening for diabetic retinopathy.**

C **Dilated direct ophthalmoscopy should only be used for opportunistic screening.**

D **Screening modalities should aim to detect sight threatening retinal disease with a sensitivity ≥80% and specificity ≥95%.**

B **Patients with ungradeable retinal photographs should receive slit lamp and indirect ophthalmoscopy examination where possible.**

D **Where possible and practical, screening should be performed at a site convenient to patients.**

6.2.3 GRADING AND QUALITY ASSURANCE

When grading retinal appearances, digital imaging is more sensitive than polaroid prints and probably similar to 35 mm film.[281] Initial data indicates that high-resolution automated techniques can identify the absence of microaneurysms on digital images with a sensitivity of 85%, although further research is required in this area to validate the technique.[282] 2+

All screening modalities should undergo quality assurance checks. For retinal photography it has been suggested that this should happen in 1% of photographs.[269] 4

C **Retinal photographs should be graded using digital images or 35 mm film by an appropriately trained grader.**

D **At least 1% of all screening events (photography or slit lamp) should be reviewed.**

The Health Technology Board for Scotland (HTBS) is carrying out a health technology assessment to determine the most efficient, effective and comprehensive national screening programme for diabetic retinopathy in Scotland.

6.3 TREATMENT

6.3.1 LASER PHOTOCOAGULATION

Laser photocoagulation for high risk retinopathy and clinically significant macular oedema (CSMO) is of proven benefit.[283,284] Older patients with diabetes and those with type 2 diabetes in particular benefit from photocoagulation before high risk features develop.[285] Laser treatment for CSMO helps to stabilise vision when used for focal or diffuse maculopathy, but was not shown to be helpful for ischaemic maculopathy.[284,286,287] It has also been shown to be effective for iris neovascularisation (rubeosis) due to microvascular disease.[288] 1++, 3

There are no clinical trial data assessing the strategy of whether treatment should be deferred in diffuse maculopathy until visual acuity is affected. There is no evidence for the use of laser in ischaemic maculopathy.

A **All patients with sight-threatening retinopathy (moderate proliferative diabetic retinopathy or worse) should receive laser photocoagulation.**

A **Patients with severe pre-proliferative or mild proliferative diabetic retinopathy should receive close follow up or laser photocoagulation.**

A **Focal or modified grid laser photocoagulation should be used for patients with focal CSMO but not for patients with ischaemic maculopathy.**

A **Diffuse maculopathy should be treated if there is a concern that the disease is progressing.**

6.3.2 VITRECTOMY

Early vitrectomy is of proven value in patients with type 1 diabetes and persistent vitreous haemorrhage for improving long term vision. Its value in type 2 diabetes is less certain. Patients with type 1 or type 2 diabetes who have severe fibrovascular proliferation with or without retinal detachment threatening the macula also have better visual acuity after vitrectomy.[289] 1+

Vitrectomy for diffuse diabetic macular oedema has been shown to result in resolution of oedema and improvement in visual acuity.[290-292] 3

B **Patients with type 1 diabetes and persistent vitreous haemorrhage should be referred for early vitrectomy.**

B **Vitrectomy should be performed for tractional retinal detachment threatening the macula and should be considered for severe fibrovascular proliferation.**

D **Vitrectomy should be considered in patients with diffuse diabetic macular oedema.**

☑ Patients with type 2 diabetes and vitreous haemorrhage which is too severe to allow photocoagulation should be referred for consideration of a vitrectomy.

6.3.3 REFERRAL INTERVALS

Delay in treatment of greater than two years from diagnosis of sight-threatening diabetic retinopathy is associated with poor outcome and severe visual loss.[283] When vitrectomy is required, a delay of over one year is associated with poorer visual outcome.[293] 1++

The Royal College of Ophthalmologists[275] recommends the following referral intervals: 4

Assess by ophthalmologist within 4 weeks if:

- there is unexplained drop in visual acuity
- there are hard exudates within 1 disc diameter of the fovea
- macular oedema is present
- there are unexplained retinal findings
- pre-proliferative or more advanced (severe) retinopathy is present.

Assess by ophthalmologist within 1 week if:

- there is new vessel formation
- there is evidence of pre-retinal and/or vitreous haemorrhage
- rubeosis iridis is present.

Assess by ophthalmologist within 1 day if:

- there is sudden loss of vision
- there is evidence of retinal detachment.

6.3.4 CATARACT EXTRACTION IN PATIENTS WITH DIABETES

Visual outcome following cataract surgery in patients with diabetes is closely linked to age and severity of retinopathy present before surgery.[294,295] Whilst postoperative progression of pre-existing proliferative diabetic retinopathy and CSMO has been documented, the balance of evidence does not show an increase in long term incidence of CSMO following cataract extraction.[294-296] 1++, 2++

B **Cataract extraction should not be delayed in patients with diabetes.**

C **Cataract extraction is advised when sight-threatening retinopathy cannot be excluded.**

C **When cataract extraction is planned in the context of advanced disease which is not stabilised prior to surgery, the risk of progression and the need for close postoperative review should be fully discussed with the patient.**

6.3.5 METHOD OF ASSESSING RETINOPATHY

Slit lamp biomicroscopy carried out by an appropriately experienced ophthalmologist is as good as the gold standard of 7-field stereoscopic photography for the assessment of CSMO.[277,284,286] 1+

Either good quality 7-field stereo photography or slit lamp biomicroscopy (both dilated) carried out by an appropriately experienced ophthalmologist should be used to investigate:

A ■ **CSMO**

B ■ **proliferative diabetic retinopathy and severe non-proliferative diabetic retinopathy.**

6.4 REHABILITATION

There is very little evidence relating to programmes of rehabilitation for patients with diabetic eye disease. Awareness of low vision aids is poor, but once available, patients benefit from being instructed in their use.

Low vision aid clinics[297] and community self-help groups[298,299] as part of a low vision service[300,301] can improve the quality of life and functional ability for patients with visual impairment. 3, 4

D **Community support, low vision aids and training in their use should be provided to people with diabetes and visual impairment.**

☑ Patients with visual impairment should be assisted to register as blind / partially sighted at an early stage.

7 Management of diabetic foot disease

7.1 EPIDEMIOLOGY AND RISK FACTORS

Based on United Kingdom population surveys, diabetic foot problems are a common complication of diabetes with prevalences of 23-42% for neuropathy, 9-23% for vascular disease and 5-7% for foot ulceration. Amputation rates are higher in patients with diabetes than non-diabetic patients.[302]

Patients with diabetes are at increased risk of peripheral vascular disease (PVD), especially when other associated risk factors are present, e.g. smoking, hypertension and hypercholesterolaemia. Diabetic foot ulceration is principally associated with PVD and peripheral neuropathy, often in combination. Other factors associated with increased risk include previous amputation,[303] previous ulceration,[304] the presence of callus,[305] joint deformity,[306] visual/mobility problems,[307] and male sex.[304] The cumulative effect of these risk factors is at least additive.[306]

7.2 CARE MANAGEMENT

Much of the evidence supporting the recommendations in this section describes specific interventions carried out with adults in a multidisciplinary context (comprising e.g. diabetes physician and specialist nurse, podiatrist, orthotist, vascular and orthopaedic surgeons) which have not been assessed in isolation. The recommendations therefore apply to comprehensive care delivered in a multidisciplinary setting to people post-puberty with diabetes.

7.2.1 PATIENT EDUCATION

Several studies of education in patients with little or no existing foot disease were identified however most of these involved very small patient numbers, used different endpoints and reported inconclusive findings. Only two large studies were identified which used significant lesions as endpoints. One indicated that, at 1 year follow up, where patients had agreed 'personalised behavioural contracts', there was a significant reduction in serious lesions.[308] The second study showed no significant change in lesions and little or no effect of a general education programme after 18 months follow up.[309] | 1^+

A single RCT suggested that intensive education may be effective in the prevention of amputation or recurrent ulceration in patients who have had previous diabetic foot disease.[310] This trial involved an unusual intervention which included frank presentation of the complications of diabetic foot disease to patients in the experimental group. This 'scare-tactic' may not be generalisable to all patient groups or settings, however the reduction in amputation and ulceration after one year was promsising and should be replicated in further trials in order to validate the technique. | 1^+

Programmes which include education with podiatry show a positive effect on minor foot problems at relatively short follow up.[311,312] | 1^+, 2^{++}

B **Foot care education is recommended as part of a multidisciplinary approach in all patients with diabetes.**

7.2.2 STRUCTURED FOOT REVIEW

The absence of reliable symptoms and the high prevalence of asymptomatic disease make foot screening essential.[302] | 4

D **All patients with diabetes should be screened for foot disease.**

There is no evidence to support the frequency of screening; however the guideline development group considers that at least annual screening from the diagnosis of diabetes is appropriate.

An example protocol for the assessment of risk of the diabetic foot is provided in figure 1 overleaf.

Figure 1

EXAMPLE PROTOCOL FOR THE ASSESSMENT OF RISK OF THE DIABETIC FOOT ADAPTED FROM THE TAYSIDE FOOT RISK ASSESSMENT PROTOCOL

Patients with diabetes should be assessed annually by a diabetologist, GP, chiropodist, diabetes nurse specialist, or practice nurse with training in diabetes to look for presence of neuropathy, ischaemia or deformity.

Patients should be categorised according to the presence of the following symptoms/signs

Normal sensation AND good pulses AND no previous ulcer AND no foot deformity AND normal vision	Loss of sensation OR absent pulses (or previous vascular surgery) OR significant visual impairment OR physical disability (e.g. stroke, gross obesity)	Previous ulcer due to neuropathy/ischaemia OR Absent pulses *and* neuropathy OR Callus with risk factor (neuropathy, absent pulse, foot deformity) OR Previous amputation	Active foot ulceration, painful neuropathy which is difficult to control.
LOW RISK	**MODERATE RISK**	**HIGH RISK**	**ACTIVE FOOT DISEASE**
▪ No specific regular chiropody input needed (except in exceptional circumstances) ▪ Patients can undertake their own nail care after appropriate education. ▪ Annual foot check	Regular (4-12 weekly) general chiropody input advised. For patients with visual impairment or physical disability, who would otherwise fit into the low risk category, input from trained Foot Care Assistants can be substituted (where available).	▪ Chiropodist with interest and expertise in diabetes either at diabetes unit or in community centre ▪ Chiropodist may want to consider orthotic referral.	Suggest making contact with local specialist diabetes team (hospital based).

In addition, patients with any of the following signs of **ischaemia** or **infection** should be considered for emergency referral to the hospital surgical receiving service or diabetic foot clinic, where appropriate:

CRITICAL ISCHAEMIA	**SEVERE INFECTION**
▪ rest or night pain ▪ pale/mottled feet ▪ dependent rubor ▪ ischaemic ulceration ▪ gangrene	▪ abscess ▪ cellulitis

Neuropathy screening can be performed either by using clinical neuropathy disability scores, 10 g monofilaments, or by use of vibration perception thresholds. All these methods, singly or in combination, have shown benefits in selecting patients at increased risk of foot ulceration.[306,313,314] 2+

C **Clinical neuropathy disability scores, 10 g monofilaments, or vibration perception thresholds are all appropriate methods for neuropathy screening.**

Methods of screening for vascular insufficiency are less well-defined. Absent pedal pulses are a guide to the presence of peripheral vascular disease and can be used for first-line screening.[315,316] 2+

Ankle pressure and pressure indices can be falsely elevated in patients with diabetes and should be interpreted with caution.[317]

7.2.3 STRUCTURED FOOT CARE

Access to a podiatrist reduces the number and size of foot calluses and improves self-care.[311] 1+

In the absence of a multidisciplinary foot care team, foot lesions are more likely to lead to amputation. Multidisciplinary foot care teams allow intensive treatment and rapid access to orthopaedic and vascular surgery. This allows control of infection and revascularisation when needed. Wound healing and foot-saving amputations can then be successfully achieved, reducing the rate of major amputations.[318-320] Adherence to locally established protocols may reduce length of stay and major complication rates.[321,322] 2+

C **All patients with diabetes should have access to structured diabetic foot care.**

7.2.4 FOOTWEAR, ORTHOSES AND TOTAL CONTACT CASTING

Plantar pressure using ordinary shoes is similar to barefoot. High-quality, cushioned-soled trainers can reduce plantar pressure more than ordinary shoes but not as much as custom-built shoes.[323,324] 2++, 3

There is limited evidence that padded hosiery can reduce peak plantar pressures.[325]

B **Patients with diabetic foot disease should be advised to wear high-quality, cushioned-soled trainers rather than ordinary shoes.**

The use of custom made foot orthoses and therapeutic footwear reduces the plantar callus thickness and incidence of ulcer relapse.[312 326-328] Patients who routinely wear their therapeutic shoes and orthoses are less likely to have ulcer relapse.[329] 1+, 2+, 3

B **Custom-built footwear or orthotic insoles should be used to reduce callus severity and ulcer recurrence.**

A single RCT showed that treatment of patients with unilateral plantar ulcers using total contact casting can reduce the healing time to a mean of approximately 6 weeks.[330-332] 1+, 2+

Use of 'half shoes' reduces the time to complete closure of the ulcer to a mean of 10 weeks.[333] 3

B **Patients who have unilateral plantar ulcers should be considered for treatment using total contact casting to optimise the healing rate of ulcers.**

7.2.5 ARTERIAL RECONSTRUCTION

Patients with diabetes are more prone to peripheral vascular disease (PVD) than patients without diabetes. This includes both proximal (aorto-iliac and femoral) and distal (calf and foot) disease. Rates of limb salvage following distal bypass surgery are relatively high. Salvage rates of around 80% are reported in the initial presence of tissue loss (gangrene and ulceration).[334] Increased frequency of distal bypass is associated with reduced frequency of amputation.[335-337] 2++

B **All patients with tissue loss and arterial disease should be considered for arterial reconstruction.**

Forefoot and midfoot pressure-reducing surgery can be safe and effective in selected groups of patients with diabetes who have non-ischaemic recurrent or refractory neuropathic ulceration at high pressure sites.[338,339] There is some evidence that pressure-reducing surgery can also be used prophylactically.[340,341] This is not standard practice in the UK and, in all cases, such surgery should only be undertaken by surgeons with specialist training. 2+, 3

No evidence was found to support recommendations on the optimum stage to make a vascular intervention, whether amputation is the best intervention in terms of quality of life, or the effectiveness of rehabilitation strategies.

7.3 TREATMENT

7.3.1 PHARMACOLOGICAL THERAPY

One RCT indicated that subcutaneous granulocyte-colony stimulating factor (g-csf) speeds up time for resolution of cellulitis in diabetic foot infections.[342] Growth factors such as topical RGD (arginine glycine aspartic acid) peptide matrix and CT-102 may increase the rate of closure of diabetic foot ulcers.[343,344] Topical becaplermin increases the rate of closure of diabetic foot ulcers.[345] 1+

A **In non-healing chronic neuropathic ulcers after optimal pressure relief, use of topical RGD peptide, CT-102 or becaplermin should be considered to speed up healing rates.**

B **Subcutaneous g-csf should be considered in the treatment of diabetic foot infections.**

No single broad spectrum antibiotic regimen was shown to be more effective over another in the treatment of diabetic foot ulcers.[346-349] 1+

There is no evidence for the optimal duration or route of antibiotic treatment in treatment of diabetic foot ulcers.

☑ Treatment of an infected diabetic foot ulcer should be commenced with a broad spectrum antibiotic regimen in conjunction with appropriate debridement. Subsequent antibiotic regimens may be modified with reference to bacteriology and clinical response.

7.3.2 TISSUE REPLACEMENT THERAPY AND MAGGOTS

Use of living human tissue replacement therapy shows a consistent increased rate of healing and increased number of completely healed ulcers in patients with diabetes. [350-352] 1+

B **Treatment of diabetic ulcers using living human tissue replacement should be considered in refractory ulcers provided the patient meets strict exclusion criteria on infection, circulation and ulcer size and depth.**

The evidence for maggot therapy is inconclusive, but clinical experience suggests that it is a useful alternative method of debridement.

7.3.3 PAINFUL DIABETIC NEUROPATHY

There is good evidence that the tricyclic antidepressants (TCAs) amitriptyline, imipramine and desipramine, the anticonvulsant carbamazepine and topical capsaicin are more effective than placebo in reducing symptoms of painful diabetic peripheral neuropathy.[353, 354] 1++

Gabapentin is superior to placebo in painful diabetic neuropathy and one RCT indicated it to have fewer side effects than TCAs.[355] 1+

A **TCAs should be used as first line therapy in painful diabetic neuropathy.**

B **Gabapentin is also recommended in painful diabetic neuropathy and is associated with fewer side effects than TCAs and older anticonvulsants.**

A **Topical capsaicin should be considered for the relief of localised neuropathic pain.**

7.3.4 CHARCOT'S FOOT

Charcot's foot is a neuroarthropathic process with osteoporosis, fracture, acute inflammation and disorganisation of foot architecture. During the acute phase, Charcot's foot can be difficult to distinguish from infection.

Clinical diagnosis of Charcot's foot is based on the appearance of a red, swollen oedematous and possibly painful foot in the absence of infection. It is associated with increased bone blood flow, osteopenia, and fracture or dislocation; however the disease process can become quiescent with increased bone formation, osteosclerosis, spontaneous arthrodesis and ankylosis.[356] | 2^{++}

Acute Charcot's foot is associated with a skin temperature 2-8°C higher than the contralateral foot as measured on thermography.[357,358] | 3

There is insufficient evidence to recommend the routine use of magnetic resonance imaging or dynamic bone scanning to distinguish acute Charcot's from osteomyelitis.

C **Diagnosis of Charcot's foot should be made by clinical examination supported, where available, by the use of thermography.**

Treatment of Charcot's foot in contact casting is associated with a reduction in skin temperature as measured by thermography and in bone activity as measured by bone isotope uptake compared to the normal foot.[358] One follow up study showed that non-weight bearing and foot protection with therapeutic shoes resulted in a healing rate of 96% in patients with diabetic foot deformities.[357] | 3

D **Total contact casting and non-weight bearing are effective treatments for acute Charcot's foot.**

There is insufficient evidence to recommend the routine use of bisphosphonates in acute Charcot's foot, although case series involving small numbers of patients indicate that they may reduce skin temperature and bone turnover in active Charcot's foot.[359,360]

8 Management of diabetes in pregnancy

8.1 INTRODUCTION

An optimal outcome may be obtained in diabetic pregnancy if excellent glycaemic control is achieved before and during pregnancy. However, type 1 diabetes is a high risk state for both the woman and her fetus. There are increased complications of diabetes, such as ketoacidosis, severe hypoglycaemia, and progression of microvascular complications. There are also increased risks of obstetric complications, such as pre-eclampsia, premature labour, spontaneous abortion, obstructed labour, polyhydramnios, and maternal infection. Fetal and neonatal complications include late intrauterine death, fetal distress, congenital malformation, hypoglycaemia, respiratory distress syndrome and jaundice. Rates of fetal and neonatal loss and major congenital malformation are increased by at least two to threefold. Type 2 diabetes is less common than type 1 diabetes during the reproductive years, but management prior to and during pregnancy should follow the same intensive programme of metabolic, obstetric and neonatal supervision.

An audit of implementation of the pilot SIGN guideline on management of diabetes in pregnancy indicated that adverse pregancy outcomes remain higher in women with diabetes than in the non-diabetic population.[361]

☑ An experienced multidisciplinary team led by a named obstetrician and physician should provide comprehensive maternity care.

Effective communication between all members of the team is essential, recognising that the key member is the woman with diabetes.

8.2 CONTRACEPTION

Contraception should be discussed on an individual basis with all women of childbearing age with diabetes. There is little evidence on choice of contraceptive method specifically in women with diabetes. In general, the contraceptive advice for a woman with diabetes should follow that in the general population but the combined oestrogen-progestogen pill should be avoided in women with complications or risk factors for vascular disease. Progestogen-only preparations may be suitable in these women, but the increased failure rate must be noted.[362,363]

The levonorgestrel-releasing intrauterine system (Mirena coil) is a safe method of contraception which may be particularly suitable for use in women with diabetes as it is as effective as sterilisation and produces low circulating hormone levels.[364] 4

☑ Pregnancy should be planned and good contraceptive advice and pre-pregnancy counselling are essential.

8.3 PRE-PREGNANCY CARE

Infants whose mothers with diabetes received dedicated multidisciplinary pre-pregnancy care show significantly fewer major congenital malformations (approximating to the rate in non-diabetic women) compared to infants of non-attending mothers. Attendance at a pre-pregnancy clinic is associated with a reduction in the rate of spontaneous abortion and in complications of pregnancy. Infants of mothers attending pre-pregnancy clinics have fewer problems and are kept in special care for shorter periods than infants of non-attending mothers.[365,366] 2+

The essential components of a pre-pregnancy care programme include review and consideration of the medical (including drug treatment), obstetric and gynaecological history; advice on glycaemic control to optimise HbA_{1c}; and screening for complications.

C **Pre-pregnancy care provided by a multidisciplinary team is strongly recommended for women with diabetes.**

☑ All healthcare professionals in contact with women with diabetes of child-bearing age should be aware of the importance of pre-pregnancy care and local arrangements for its delivery, and should share this information with the woman.

8.4 NUTRITIONAL MANAGEMENT

It is good clinical practice to provide dietary advice to women before, during and after pregnancy.[367] | 4

D **Dietetic advice should be available in all diabetic antenatal clinics, and should encourage diets with high levels of complex carbohydrates, soluble fibre and vitamins, and reduced levels of saturated fats.**

Neural tube defects in high risk pregnancies are associated with lower levels of folate.[368] A large study in non-diabetic women has shown that prescription of 4 mg folate supplementation pre- and peri-conceptually confers protection against neural tube defects, particularly in women at high risk.[369] | 1^{++}, 2^{++}

B **All women with diabetes should be prescribed pre-pregnancy folate supplementation (c. 4 mg), continuing up to 12 weeks gestation.**

☑ Folic acid 5 mg tablets are readily available, suitable, and should be provided wherever pre-pregnancy care is delivered.

8.5 OPTIMISATION OF GLYCAEMIC CONTROL

Optimal glucose control before and during pregnancy reduces congenital malformations, stillbirth, neonatal hypoglycaemia, and respiratory distress syndrome. Women should aim to maintain blood glucose as near to the non-diabetic range as possible without excessive risk of hypoglycaemia.[370] This usually means targeting levels between 4 and 7 mmol/l. Diabetes specialist nurses and midwives have an important role in educating women on the need for home blood glucose monitoring (4-6 times a day) and intensive insulin regimens. Intensive basal bolus regimens are commonly used and insulin analogues are increasingly used, although published research on their role and safety in pregnancy is limited. | 4

D **Before and during pregnancy, women with diabetes should aim to have blood glucose between 4 and 7 mmol/l.**

8.6 COMPLICATIONS DURING PREGNANCY

8.6.1 OBSTETRIC COMPLICATIONS

There is no specific evidence on management of obstetric complications, including pregnancy-induced hypertension and increased risk of thromboembolism, in women with diabetes. These risks should be managed as for other pregnant women.

8.6.2 METABOLIC COMPLICATIONS

During pregnancy, hypoglycaemic unawareness and severe hypoglycaemia are common and diabetic ketoacidosis can develop more rapidly. Women and their partners need education on the management of hypoglycaemia, including the use of glucagon, and on the recognition and prevention of ketoacidosis, which may result in fetal death. Local emergency contact arrangements must be explicit.

8.6.3 MICROVASCULAR COMPLICATIONS

Diabetic retinal and renal disease can deteriorate during pregnancy.[371] The presence of retinopathy alone is not associated with a poorer pregnancy outcome for the fetus unless concurrent nephropathy is evident.[372] | 2^{+}, 3

Retinopathy

In one study, 77.5% of women with baseline retinopathy showed progression during pregnancy, with 22.5% requiring panretinal photocoagulation.[373] Poor glycaemic control in the first trimester and pregnancy-induced or chronic hypertension are independently associated with the progression of retinopathy.[371] 2+

C **Fundal examination prior to conception and during each trimester is advised. More frequent assessment may be required in those with poor glycaemic control or hypertension.**

C **Early referral of pregnant women with moderate retinopathy to an ophthalmologist is recommended due to the potential for rapid development of neovascularisation.**

Parous women with type 1 diabetes have significantly lower levels of all retinopathy compared with nulliparous.[374] The associated significant difference in HbA_{1c} suggests that improved glycaemic control associated with pregnancy may be sustained over time, with beneficial effects on long term complications. 2+

C **Women should be reassured that tight glycaemic control during and immediately after pregnancy can effectively reduce the long term risk of retinopathy in future.**

Nephropathy

There is an association between pre-existing nephropathy (microalbuminuria or albuminuria) and a poorer pregnancy outcome, though this is not due to any increase in congenital malformations. Proteinuria increases transiently during pregnancy, returning to the pre-pregnancy level within three months of delivery. The incidence of worsening chronic hypertension or pregnancy-induced hypertension / pre-eclampsia is high (varying from 40% to 73% across series) in women with both incipient and overt nephropathy. Worsening nephropathy and superimposed pre-eclampsia are the most common causes of pre-term delivery in women with diabetes.

☑ The management of pregnant women with diabetic nephropathy should follow the recommendations in section 5 (target blood pressure <140/80 mm Hg). However, ACE inhibitors should be avoided as they may adversely affect the fetus. Appropriate antihypertensive agents which may be used during pregnancy include methyl dopa, labetalol and nifedipine.

8.7 FETAL MONITORING

Diabetic pregnancies are at high risk, therefore regular monitoring is appropriate. The risk is greater in women with complications of diabetes (e.g. vascular or renal disease) or of pregnancy (e.g. pre-eclampsia).[375] 3

The clinical judgement of an obstetrician experienced in diabetic pregnancy is essential and ultrasound scanning must be available for assessing gestational age, examining for congenital abnormalities and monitoring fetal growth. No evidence has been identified on the effectiveness of any single technique, and the most reliable method for fetal monitoring may involve the use of more than one technique. A suggested minimum monitoring provision in the third trimester involves weekly clinical assessment and regular cardiotocography. Women should be encouraged to report any perceived reduction in fetal movement during pregnancy.

The use of Doppler ultrasound in high risk pregnancies appears to improve a number of obstetric care outcomes and appears promising in helping to reducing perinatal deaths.[376] 1++

8.8 DELIVERY

National audit data in Scotland indicate that delivery in women with diabetes is generally expedited within 40 weeks gestation.[361] No clear evidence was identified to inform the optimal timing for delivery. The timing of delivery should be determined on an individual basis. 3

Women with diabetes in pregnancy who are at risk of pre-term delivery should receive antenatal corticosteroids in line with local protocols.[377] If steroids are clinically indicated for pre-term labour, inpatient supervision by an experienced team is essential to regulate diabetic control. 1++

Women with diabetes have a high rate of caesarean section even after controlling for confounding factors.[378] Estimated fetal weight >4.5 kg is generally regarded as an indication for delivery by elective caeserean section.[379] 2+, 4

☑
- Women with insulin-requiring diabetes in pregnancies which are otherwise progressing normally should be assessed at 38 weeks gestation to ensure delivery by 40 weeks.
- Women with diabetes should be delivered in consultant-led maternity units which have a senior physican, obstetrician, and neonatologist available.
- The progress of labour should be monitored as for other high risk women, including continuous electronic fetal monitoring.
- Intravenous insulin and dextrose should be administered as necessary to maintain blood glucose levels between 4 and 7 mmol/l.

8.9 INFANTS OF MOTHERS WITH DIABETES

Labour and delivery should only be undertaken in a maternity unit supported by neonatal intensive care facilities. A paediatrician skilled in resuscitation should be present at the delivery of all women with diabetes, but there is no need for routine admission of the infant to the neonatal unit. There is insufficient evidence on the preferred method of cotside blood glucose measurement in neonates; however, whichever method is used, the glucose value should be confirmed by laboratory measurement. Neonatal hypoglycaemia is defined at blood glucose <2.6 mmol/l and is associated with adverse short and long term neurodevelopmental outcomes.[380] 4

☑ Early feeding is advised to avoid neonatal hypoglycaemia and to stimulate lactation.

Six-week post partum fasting plasma glucose levels of women with type 1 diabetes, who exclusively breast fed, have been found to be significantly lower than those who bottle fed.[381] There are well-documented health benefits for infants that are breast-fed. 2++

B **Breast feeding is recommended for infants of mothers with diabetes, but mothers should be supported in the feeding method of their choice.**

8.10 POSTNATAL CARE

Women with type 1 or type 2 diabetes may require adjustment of their treatment regimen postnatally. Women with gestational diabetes should be investigated postnatally to clarify the diagnosis and exclude type 1 or type 2 diabetes. The opportunity should also be taken to provide lifestyle advice to reduce the risk of subsequent type 2 diabetes.

☑ Postnatal follow up should be seen as an opportunity to initiate pre-pregnancy care for any subsequent pregnancy. Appropriate contraception should be provided and the importance of good glycaemic control emphasised.

8.11 GESTATIONAL DIABETES

There is no consensus on the definition, management or treatment of gestational diabetes (GDM). GDM can be defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy.[3] This definition will include women with abnormal glucose tolerance that reverts to normal after delivery, those with undiagnosed type 1 or type 2 diabetes, and rarely women with monogenic diabetes.[382] If type 1 or type 2 diabetes is presumed (e.g. due to early presentation or grossly elevated blood glucose), urgent action is required to normalise metabolism. The most appropriate strategies for screening, diagnosing and managing asymptomatic GDM remain controversial.

8.11.1 SCREENING FOR GDM

An important aim of screening in pregnancy is to identify women with undiagosed type 1 or type 2 diabetes. Screening for GDM requires urine to be tested for glycosuria at every antenatal visit. A random venous plasma glucose should be recorded if 2+ glycosuria is detected, and routinely at 28 weeks gestation. The World Health Organisation advise that a 75 g oral glucose tolerance test (OGTT) should be carried out if the blood glucose is >5.5 mmol/l two hours or more after food, or >7 mmol/l within two hours of food.

8.11.2 DIAGNOSIS OF GDM

The diagnostic label of GDM is associated with an increased likelihood of induction of labour, instrumental delivery and caesarean section. Accurate diagnosis is therefore important, but is hampered by the poor reproducibility of the OGTT during pregnancy.[383] The criteria recommended for diagnosis of GDM are fasting venous plasma glucose >5.5 mmol/l or two hours after OGTT >9 mmol/l.[384] 2^+, 4

A diagnosis of GDM identifies women at increased risk of developing type 2 diabetes in future.[385]

8.11.3 MANAGEMENT OF GDM

Impaired glucose tolerance is associated with macrosomia.[386] Dietary management, with or without insulin, causes a modest but consistent reduction in birth weight. However, intensive treatment with diet or insulin may compromise babies of mothers with gestational diabetes that are not macrosomic.[387] 2^{++}

If blood glucose levels are in the range for established diabetes (*see section 1.5*), intensive specialist management is required.

If, after nutritional advice, pre- and post-prandial glucose levels are normal and there is no evidence of excessive fetal growth, manage as a normal pregnancy.

If, after a trial of dietary intervention, fasting glucose levels exceed 6 mmol/l and 2-hour post-prandial levels exceed 7 mmol/l with evidence of macrosomia on ultrasound (>95th centile), intensive management with diet, blood glucose monitoring and insulin are appropriate.[388]

B **Women with gestational diabetes should receive intensive management with diet and/or insulin if macrosomia is suspected or if blood glucose levels are in the range for established diabetes.**

9 Development of the guideline

9.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other health care professionals, and patient organisations, funded by the Clinical Resource and Audit Group (CRAG) of the Scottish Executive Health Department. SIGN guidelines are developed by multidisciplinary groups using a standard methodology, based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in SIGN 50: A guideline developer's handbook, available at **www.sign.ac.uk.**

9.2 THE GUIDELINE DEVELOPMENT GROUPS

The guideline was developed by seven multidisciplinary development groups coordinated by a steering group comprising the leaders of each of the groups, chaired by Professor Ian Campbell, Consultant Physician, Victoria Hospital, Kirkcaldy. Declarations of interest were made by all members of the guideline development groups. Guideline development and literature review expertise, support, and facilitation were provided by the SIGN Executive, in particular: Miss Francesca Chappell, Information Officer; Mr Robin Harbour, Information Manager; Dr Moray Nairn, Programme Manager; and Mr Alex Haig, formerly Information Officer, Royal College of Physicians of Edinburgh.

9.3 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by the SIGN Information Team. All searches covered systematic reviews, meta-analyses, and randomised controlled trials. Where appropriate, searches were extended to cover observational studies. Due to the wide subject coverage of these guidelines, a large number of topic-specific searches were required. All searches covered the Cochrane Library, Embase, Healthstar, and Medline. In appropriate cases searches were extended to cover CINAHL and Psychinfo. All searches covered the period 1991-2000. Searches for the section on children and young people were extended back to 1980. Internet searches were carried out on the Web sites of the Canadian Practice Guidelines Infobase, the New Zealand Guidelines Programme, and US National Guidelines Clearinghouse. Searches were also carried out on the search engines Northern Light and OMNI, and all suitable links followed up.

The Medline version of the main search strategies and notes on the coverage of ancillary searches can be found on the SIGN Website, in the section covering supplementary guideline material. The main searches were supplemented by material identified by individual members of the development group. All selected papers were evaluated using standard methodological checklists before conclusions were considered as evidence.

9.4 CONSULTATION AND PEER REVIEW

A national open meeting is the main consultative phase of SIGN guideline development, at which the guideline development group presents its draft recommendations for the first time. The national open meeting for this guideline was held at the Royal College of Physicians of Edinburgh on 11 December 2000. The draft guideline was also available on the SIGN website for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

The guideline was reviewed in draft form by a panel of independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. SIGN is very grateful to all of these experts for their contribution to this guideline. The specialist reviewers and Editorial Group for this guideline are listed on the SIGN website at **www.sign.ac.uk**.

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Abbreviations

AIRE	Acute Infarction Ramipril Efficacy
4S	Scandinavian Simvastatin Study
ACE	Angiotensin-converting enzyme
ACR	albumin/creatinine ratio
AER	albumin excretion rate
BARI	Bypass Angioplasty Revascularisation Investigation
BMI	body mass index
CABG	Coronary Artery Bypass Grafting
CI	confidence interval
CONSENSUS	Co-operative North Scandinavian Enalapril Survival Study
CRAG	Clinical Resource and Audit Group
CSMO	clinically significant macular oedema
CVD	cardiovascular disease
DCCT	Diabetes Control and Complication Trial
DIPP	Finnish IDDM Prediction and Prevention Project
DPP	Diabetes Prevention Program
DPT-1	Diabetes Prevention Trial
EAST	Emory Angioplasty vs Surgery Trial
ENDIT	European Nicotinamide Diabetes Intervention Trial
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
g- csf	granulocyte-colony stimulating factor
GDM	gestational diabetes mellitus
GFR	glomerular filtration rate
GP	general practitioner
HbA_{1c}	haemoglobin A_{1c}
HDL	high density lipoprotein
HEBS	Health Education Board for Scotland
HOPE	Heart Outcomes Prevention Evaluation
HOT	Hypertension Optimal Treatment
HTBS	Health Technology Board for Scotland
IFG	Impaired Fasting Glycaemia
IGT	Impaired Glucose Tolerance
LDL	Low density lipoprotein
MI	myocardial infarction
NHS	National Health Service
NRT	nicotine replacement therapy
OGTT	oral glucose tolerance test
PVD	peripheral vascular disease
RCT	randomised controlled trial
RGD	arginine glycine aspartic acid
SIGN	Scottish Intercollegiate Guidelines Network
SOLVD	Studies of Left Ventricular Dysfunction
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
UKPDS	United Kingdom Prospective Diabetes Study
WHO	World Health Organisation