

**116**

Management of diabetes

A national clinical guideline



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, eg case reports, case series
4	Expert opinion

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the 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

- | | |
|-------------------------------------|---|
| <input checked="" type="checkbox"/> | Recommended best practice based on the clinical experience of the guideline development group |
|-------------------------------------|---|

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Scottish Intercollegiate Guidelines Network

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1 Introduction

1.1 THE NEED FOR A GUIDELINE

Diabetes mellitus is a major cause of morbidity and mortality in Scotland and worldwide, with an increasing prevalence. In 2009 there were around 228,000 people registered as having diabetes in Scotland, an increase of 3.6% from the preceding year.¹ This increase relates, in part, to the increasing age of the population, an increase in obesity and also perhaps to increasing survival of those with diabetes.

Twenty years ago the St Vincent declaration aimed to decrease blindness, end-stage renal failure, amputation and cardiovascular disease in those with diabetes and to improve the outcome of pregnant mothers who have diabetes. Since that time there has been a great increase in evidence showing that many diabetic outcomes can be influenced by appropriate therapies. Part of this evidence base was reviewed in the previous SIGN guideline on management of diabetes (SIGN 55) published in 2001.² New clinical evidence has been published since then and has resulted in the need for this selective update. Implementing the evidence described in this guideline will have a positive effect on the health of people with diabetes.

1.1.1 UPDATING THE EVIDENCE

Since the publication of SIGN 55, new evidence has been published in many areas covered by the recommendations in that guideline. Where this evidence was thought likely to significantly change either the content or grading of these recommendations, it has been identified and reviewed. Where new evidence does not update existing recommendations and where no new evidence was identified to support an update, the guideline text and recommendations are reproduced verbatim from SIGN 55. The original supporting evidence was not re-appraised by the current guideline development group. A number of new areas that were not considered in SIGN 55 have also been incorporated into this selective update, including entirely new sections on glucose-lowering agents for people with type 2 diabetes and psychosocial factors (see section 1.2.3).

A Cost and Resource Impact Assessment report developed by NHS QIS is available as a companion document to this guideline. This document reports the national costs to NHSScotland of implementing recommendations that are estimated to have a net additional cost of £5 million or more to introduce.

1.2 REMIT OF THE GUIDELINE

1.2.1 OVERALL OBJECTIVES

This guideline provides recommendations based on current evidence for best practice in the management of diabetes. For people with type 1 and type 2 diabetes recommendations for lifestyle interventions are included, as are recommendations for the management of cardiovascular, kidney and foot diseases. Guidance for all people with diabetes to prevent visual impairment, and specific advice for pregnant women with diabetes is provided. A new section on the management of psychosocial issues, drawn partially from evidence originally contained in other sections, is now included. Finally, a section on the management of type 1 diabetes and a new section on glucose-lowering therapies in people with type 2 diabetes have been added. Implementation of these recommendations will encourage the provision and development of high quality care for people with diabetes. It should also inform the development of measureable standards of diabetes care. Prevention of diabetes and pre-diabetes are not covered.

1.2.2 TARGET USERS OF THE GUIDELINE

This guideline will mainly be of interest to all healthcare professionals involved in the care of people with diabetes. The target users are, however, much broader than this, and include people with diabetes, their carers and those who interact with people with diabetes outside of the NHS. It will also be of interest to those planning the delivery of services in NHSScotland and beyond.

1.2.3 SUMMARY OF UPDATES TO THE GUIDELINE, BY SECTION

2	Key recommendations	New
3	Lifestyle management	Updated
4	Psychosocial factors	Updated
5	Management of type 1 diabetes	Updated
6	Pharmacological management of glycaemic control in people with type 2 diabetes	New
7	Management of diabetes in pregnancy	Updated
8	Management of diabetic cardiovascular disease	Updated
9	Management of kidney disease in diabetes	Updated
10	Prevention of visual impairment	Updated
11	Management of diabetic foot disease	Minor update
12	Provision of information	New

1.3 DEFINITIONS

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

The World Health Organization (WHO)³ advises that the range of blood glucose indicative of diabetes mellitus is as follows:

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

The fact that glycated haemoglobin (HbA1c) reflects average plasma glucose over the previous two to three months in a single measure which can be performed at any time of the day and does not require any special preparation such as fasting has made it a key measure for assessing glycaemic control in people with established diabetes. In 2006 the WHO considered HbA1c as a candidate diagnostic tool for diabetes. They reported that HbA1c measurement is not widely available in many countries throughout the world and there are aspects of its measurement which are problematic.³ The HbA1c result is influenced by several factors including anaemia, abnormalities of haemoglobin, pregnancy and uraemia. Some of these factors may be a bigger problem in under-resourced countries due to a higher prevalence of anaemia and of haemoglobinopathies. At the time of publication HbA1c was not recommended as a diagnostic test for diabetes, but there is ongoing work to standardise HbA1c reporting worldwide which may lead to further developments in the role of HbA1c.

**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 Glucose (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 and/or future diabetes.

Until June 2009 glycated haemoglobin in the UK was reported in Diabetes Control and Complication Trial (DCCT)-aligned format with the units being the proportion of total haemoglobin that is glycosylated expressed as a percentage. While UK laboratories standardised measures of HbA1c so that results were aligned with the analyses used in the DCCT, laboratories in other countries did not necessarily do so meaning that HbA1c values could not be accurately compared worldwide. Furthermore, since the DCCT, the methods used for measuring HbA1c have been found to have interferences yielding a falsely high result. A new and more accurate standard published by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) replaces the DCCT-aligned calibration for HbA1c and reports results in mmol/mol.⁴ To facilitate the changeover of measurements both formats will be reported in parallel from June 2009 to June 2011, and the IFCC format only thereafter (see Annex 2). In this guideline, HbA1c values will be presented as DCCT-aligned values in text or recommendations with IFCC calibration in brackets, eg HbA1c = 7.5% (59 mmol/mol).

1.4 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of 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. Adherence to guideline recommendations 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 must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, 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.

1.4.1 PATIENT VERSION

A patient version of this guideline is available from the SIGN website, www.sign.ac.uk

1.4.2 PRESCRIBING OF LICENSED MEDICINES OUTWITH THEIR MARKETING AUTHORISATION

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (product licence). This is known as 'off label' use. It is not unusual for medicines to be prescribed outwith their product licence and this can be necessary for a variety of reasons.

Generally the unlicensed use of medicines becomes necessary if the clinical need cannot be met by licensed medicines; such use should be supported by appropriate evidence and experience.⁵

Medicines may be prescribed outwith their product licence in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose.

'Prescribing medicines outside the recommendations of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability. The prescriber should be able to justify and feel competent in using such medicines.'⁵

Any practitioner following a SIGN recommendation and prescribing a licensed medicine outwith the product licence needs to be aware that they are responsible for this decision, and in the event of adverse outcomes, may be required to justify the actions that they have taken.

Prior to prescribing, the licensing status of a medication should be checked in the current version of the British National Formulary (BNF).

1.4.3 ADDITIONAL ADVICE TO NHSSCOTLAND FROM NHS QUALITY IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

NHS QIS processes multiple technology appraisals (MTAs) for NHSScotland that have been produced by the National Institute for Health and Clinical Excellence (NICE) in England and Wales.

The Scottish Medicines Consortium (SMC) provides advice to NHS Boards and their Area Drug and Therapeutics Committees about the status of all newly licensed medicines and any major new indications for established products.

SMC advice and NHS QIS validated NICE MTAs relevant to this guideline are summarised in the section on implementation.

2 Key recommendations

The following recommendations were highlighted by the guideline development group as the key clinical recommendations that should be prioritised for implementation. The grade of recommendation relates to the strength of the supporting evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

2.1 LIFESTYLE MANAGEMENT

- A** Adults with type 1 diabetes experiencing problems with hypoglycaemia or who fail to achieve glycaemic targets should have access to structured education programmes based upon adult learning theories.
- A** Adults with type 2 diabetes should have access to structured education programmes based upon adult learning theories.
- B** All people who smoke should be advised to stop and offered support to help facilitate this in order to minimise cardiovascular and general health risks.
- A** Obese adults with type 2 diabetes should be offered individualised interventions to encourage weight loss (*including lifestyle, pharmacological or surgical interventions*) in order to improve metabolic control.
- Self monitoring of blood glucose may be considered in the following groups of patients with type 2 diabetes who are not using insulin:
 - those at increased risk of hypoglycaemia
 - those experiencing acute illness
 - those undergoing significant changes in pharmacotherapy or fasting, for example, during Ramadan
 - those with unstable or poor glycaemic control (HbA1c > 8.0% (64 mmol/mol))
 - those who are pregnant or planning pregnancy.

2.2 PSYCHOSOCIAL FACTORS

- B** Regular assessment of a broad range of psychological and behavioural problems in children and adults with type 1 diabetes is recommended.
 - In children this should include eating disorders, behavioural, emotional and family functioning problems.
 - In adults this should include anxiety, depression and eating disorders.
- A** Children and adults with type 1 and type 2 diabetes should be offered psychological interventions (*including motivational interviewing, goal setting skills and CBT*) to improve glycaemic control in the short and medium term.

2.3 MANAGEMENT OF TYPE 1 DIABETES

- B** An intensified treatment regimen for adults with type 1 diabetes should include either regular human or rapid-acting insulin analogues.
- B** Basal insulin analogues are recommended in adults with type 1 diabetes who are experiencing severe or nocturnal hypoglycaemia and who are using an intensified insulin regimen. Adults with type 1 diabetes who are not experiencing severe or nocturnal hypoglycaemia may use basal analogues or NPH insulin.
- B** Children and adolescents may use either insulin analogues (*rapid-acting and basal*), regular human insulin and NPH preparations or an appropriate combination of these.
- C** The insulin regimen should be tailored to the individual child to achieve the best possible glycaemic control without disabling hypoglycaemia.
- A** CSII therapy is associated with modest improvements in glycaemic control and should be considered for patients unable to achieve their glycaemic targets.
- B** CSII therapy should be considered in patients who experience recurring episodes of severe hypoglycaemia.
- 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.

2.4 PHARMACOLOGICAL MANAGEMENT OF GLYCAEMIC CONTROL IN PEOPLE WITH TYPE 2 DIABETES

- A** An HbA1c target of 7.0% (*53 mmol/mol*) among people with type 2 diabetes is reasonable to reduce risk of microvascular disease and macrovascular disease. A target of 6.5% (*48 mmol/mol*) may be appropriate at diagnosis. Targets should be set for individuals in order to balance benefits with harms, in particular hypoglycaemia and weight gain.
- A** DPP-4 inhibitors may be used to improve blood glucose control in people with type 2 diabetes.
- A** GLP-1 agonists (*exenatide or liraglutide*) may be used to improve glycaemic control in obese adults (*BMI ≥ 30 kg/m²*) with type 2 diabetes who are already prescribed metformin and/or sulphonylureas. A GLP-1 agonist will usually be added as a third line agent in those who do not reach target glycaemia on dual therapy with metformin and sulphonylurea (*as an alternative to adding insulin therapy*).
- A** Oral metformin and sulphonylurea therapy should be continued when insulin therapy is initiated to maintain or improve glycaemic control.
- A** When commencing insulin therapy, bedtime basal insulin should be initiated and the dose titrated against morning (*fasting*) glucose. If the HbA1c level does not reach target then addition of prandial insulin should be considered.
- A** Once daily bedtime NPH insulin should be used when adding insulin to metformin and/or sulphonylurea therapy. Basal insulin analogues should be considered if there are concerns regarding hypoglycaemia risk.
- A** Soluble human insulin or rapid-acting insulin analogues can be used when intensifying insulin regimens to improve or maintain glycaemic control.

2.5 MANAGEMENT OF DIABETES IN PREGNANCY

- C** Pre-pregnancy care provided by a multidisciplinary team is strongly recommended for women with diabetes.
- A** A suitable programme to detect and treat gestational diabetes should be offered to all women in pregnancy.
- A** Pregnant women with GDM should be offered dietary advice and blood glucose monitoring and be treated with glucose-lowering therapy depending on target values for fasting and postprandial targets.
- B** Metformin or glibenclamide may be considered as initial pharmacological, glucose-lowering treatment in women with gestational diabetes.

2.6 MANAGEMENT OF DIABETIC CARDIOVASCULAR DISEASE

- A** Hypertension in people with diabetes should be treated aggressively with lifestyle modification and drug therapy.
- A** Target diastolic blood pressure in people with diabetes is ≤ 80 mm Hg.
- D** Target systolic blood pressure in people with diabetes is < 130 mm Hg.
- A** Lipid-lowering drug therapy with simvastatin 40 mg or atorvastatin 10 mg is recommended for primary prevention in patients with type 2 diabetes aged > 40 years regardless of baseline cholesterol.
- A** Intensive lipid-lowering therapy with atorvastatin 80 mg should be considered for patients with diabetes and acute coronary syndromes, objective evidence of coronary heart disease on angiography or following coronary revascularisation procedures.

2.7 MANAGEMENT OF KIDNEY DISEASE IN DIABETES

- A** Reducing proteinuria should be a treatment target regardless of baseline urinary protein excretion. However, patients with higher degrees of proteinuria benefit more. There should be no lower target as the greater the reduction from baseline urinary protein excretion, the greater the effect on slowing the rate of loss of GFR.
- A** In people with diabetes and kidney disease, blood pressure should be reduced to the lowest achievable level to slow the rate of decline of glomerular filtration rate and reduce proteinuria.
- A** People with type 1 diabetes and microalbuminuria should be treated with an ACE inhibitor irrespective of blood pressure.
- A** People with type 2 diabetes and microalbuminuria should be treated with an ACE inhibitor or an ARB irrespective of blood pressure.
- A** ACE inhibitors and/or ARBs should be used as agents of choice in patients with chronic kidney disease and proteinuria (≥ 0.5 g/day, approximately equivalent to a protein/creatinine ratio of 50 mg/mmol) to reduce the rate of progression of chronic kidney disease.

2.8 PREVENTION OF VISUAL IMPAIRMENT

- A** Good glycaemic control (*HbA1c ideally around 7% or 53 mmol/mol*) and blood pressure control (*< 130/80 mm Hg*) should be maintained to prevent onset and progression of diabetic eye disease.
- B** Systematic screening for diabetic retinal disease should be provided for all people with diabetes.
- A** All people with type 1 or type 2 diabetes with new vessels at the disc or iris should receive laser photocoagulation. Laser photocoagulation should also be provided for patients with new vessels elsewhere with vitreous haemorrhage. All people with type 2 diabetes and new vessels elsewhere should receive laser photocoagulation.

2.9 MANAGEMENT OF DIABETIC FOOT DISEASE

- B** All patients with diabetes should be screened to assess their risk of developing a foot ulcer.
- C** Patients with active diabetic foot disease should be referred to a multidisciplinary diabetic foot care service.

3 Lifestyle management

Modification of adverse lifestyle factors is an important aspect of the management of all types of 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, eg smoking. However, helping patients to modify certain behaviours should take account of other factors such as the patient's willingness to change, their perception of their diabetes, and factors which may be indirectly 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, structured education, self monitoring of glycaemic control, and the specific areas of smoking, obesity, physical activity, healthy eating and alcohol. Some recommendations in 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 - including telephone contact, multiple injections of insulin and self monitoring of blood glucose have led to improvements in self-management.⁶
- Computer-assisted programmes which provide education and trigger self-management have a proven benefit in terms of both metabolic and psychosocial outcomes.^{7,8}
- Psychological interventions which are varied and include behaviour modification, motivational interviewing, patient empowerment and activation have a positive impact on outcomes (see section 4).
- Interventions based on a theoretical model or knowledge base have better outcomes.

1++
1+
2++

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

B Computer-assisted education packages and telephone prompting should be considered as part of a multidisciplinary lifestyle intervention programme.

No evidence was identified to determine the optimal setting of lifestyle interventions, nor which addresses long term (> 1 year) follow up in educational interventions.

Telephone or postal reminders prompting people with diabetes to attend clinics or appointments are an effective method of improving attendance.^{9,10}

1+
4

3.1.2 TRAINING HEALTH PROFESSIONALS TO DELIVER LIFESTYLE INTERVENTIONS

A randomised controlled trial (RCT) conducted in primary care indicated that patient satisfaction and knowledge improve when lifestyle interventions are delivered by staff who have been trained to take a patient-centred approach.¹¹

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.¹²

3

B Healthcare professionals should receive training in patient-centred interventions in diabetes.

3.2 STRUCTURED EDUCATION

Educational interventions for diabetes are complex and varied. A Patient Education Working Group convened by the Department of Health and Diabetes UK has laid out the criteria for the development of high quality patient education programmes. These key criteria have been endorsed by a Health Technology Assessment (HTA).¹³ The key standards are:

- Any programme should have an underpinning philosophy, should be evidence based, and suit the needs of the individual. The programme should have specific aims and learning objectives, and should support the development of self-management attitudes, beliefs, knowledge and skills for the learner, their family and carers.
- The programme should have a structured curriculum which is theory driven, evidence based, resource effective, have supporting materials and be written down.
- It should be delivered by trained educators who have an understanding of the educational theory appropriate to the age and needs of the programme learners, and be trained and competent in delivery of the principles and content of the specific programme they are offering.
- The programme should be quality assured, be reviewed by trained, competent, independent assessors and be assessed against key criteria to ensure sustained consistency.
- The outcomes from the programme should be regularly audited.

Research in this area is difficult to carry out and does not lend itself well to traditional randomised controlled intervention trials. Many studies have included “wait list” control groups where the intervention group is compared with a similar group who receive the same intervention but delayed by a period of time. In addition, whilst measurement of HbA1c is the most commonly used method to assess glycaemic control, many different aspects of quality of life have been assessed using a number of different assessment tools.

The lack of head-to-head comparative trials renders it impossible to recommend one specific programme over any other. It is important to consider the outcomes that are desirable for the population being treated and to consider whether the trial data support the delivery of those outcomes for that population.

- Structured education programmes should adhere to the principles laid out by the Patient Education Working Group.

3.2.1 STRUCTURED EDUCATION IN ADULTS WITH TYPE 1 DIABETES

Structured education based on principles of adult learning (including patient empowerment and experiential learning) is associated with improved psychological well-being, reduced anxiety and overall improvement in quality of life in people with type 1 diabetes.¹⁴⁻¹⁷ The effect of structured education on glycaemic control in people with type 1 diabetes varies across different programmes.

1++
1+

In recent years the DAFNE (Dose Adjustment for Normal Eating) education programme has been introduced for adults with type 1 diabetes. Patients taking part in the DAFNE programme obtained an average 1% improvement in HbA1c after six months.¹⁴ In addition patients noted overall improvement in quality of life and improved dietary freedom. No effect was noted in frequency of severe hypoglycaemia or patient-perceived hypoglycaemia.

1++

DAFNE is likely to be cost effective adding 0.063 quality adjusted life years (QALY), and saving £536 per patient treated discounted over 10 years compared with conventional treatment.¹⁸

1++

One RCT evaluating BITES (Brief Educational Intervention in Type 1 Diabetes) included adults with type 1 diabetes who attended a 2.5 day course delivered over six weeks.¹⁹ People taking part in this programme described increased treatment satisfaction at up to 12 months, however no benefit was observed in terms of HbA1c, rates of hypoglycaemia, blood pressure, lipids, weight, BMI or use of insulin.

1+

Preliminary results for BERTIE, a structured education programme for people with newly diagnosed or established diabetes, have been published.²⁰ This retrospective observational study showed HbA1c (mean \pm standard error, SE) fell from $8.9 \pm 0.2\%$ (74 ± 2 mmol/mol) to $8.4 \pm 0.2\%$ (68 ± 2 mmol/mol) ($p < 0.001$) at three months, and was maintained at six months, $8.6\% \pm 0.3$ (70 ± 3 mmol/mol), at 12 months and $8.3\% \pm 0.5$ (67 ± 5 mmol/mol) at 24 months. The programme occupies about 7.5 hours direct health professional contact per person, spread over a month and may be more easily delivered within routine clinical services than programmes requiring more intensive input. Further evaluation of people with different baseline glycaemic control using a controlled methodology and assessing further critical outcomes, including hypoglycaemia, is required.

3

A number of structured education programmes have been developed specifically for patients who have significant problems with hypoglycaemia. These include Hypoglycaemia Anticipation, Awareness and Treatment Training (HAATT),²¹ HyPOS²² and Blood Glucose Awareness Training (BGAT).²³ Improvements in hypoglycaemia rates and awareness seen in these programmes are not associated with deterioration in overall glycaemic control.

1⁺⁺

A Adults with type 1 diabetes experiencing problems with hypoglycaemia or who fail to achieve glycaemic targets should have access to structured education programmes based upon adult learning theories.

3.2.2 STRUCTURED EDUCATION IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES

Structured education based on developing problem solving skills targeted at children and adolescents has a positive effect on a number of behavioural outcomes (including frequency of self monitoring of blood glucose, better compliance with sick-day rules, increased levels of exercise, dietary intake and improved medication adherence) and overall quality of life.²⁴⁻²⁶ There is limited evidence for a small reduction in HbA1c (approximately 0.3% (3 mmol/mol)).^{16,24}

1⁺2⁺

No evidence was identified to indicate whether group or individualised (one-to-one) structured education is associated with better outcomes.

B Children and adolescents should have access to programmes of structured education which have a basis in enhancing problem solving skills.

3.2.3 STRUCTURED EDUCATION IN PEOPLE WITH TYPE 2 DIABETES

Structured education based on principles of adult learning (including patient empowerment and experiential learning) is associated with improved psychological well-being, reduced anxiety and overall improvement in quality of life in patients with type 2 diabetes.^{13,27-29}

1⁺⁺1⁺

Structured education programmes for patients with type 2 diabetes show variable effects on glycaemic control. Most education interventions are associated with some HbA1c improvement but this is not a universal finding. HbA1c changes vary with the interventions used but, where benefit is seen, the magnitude of change is usually in the range of 0.3 (3 mmol/mol) to 1.0% (11 mmol/mol) improvement.^{14,15,30-33}

1⁺⁺

One systematic review compared the effect of individual structured education delivered face to face against usual care in adults with type 2 diabetes.³⁴ Individual education did not significantly improve glycaemic control (weighted mean difference (WMD) in HbA1c -0.1% (-1 mmol/mol), 95% CI -0.3 (-3) to 0.1 (1), $p = 0.33$) over a 12 to 18 month period. In a subgroup analysis of studies involving participants with a higher mean baseline HbA1c ($> 8\%$ (64 mmol/mol)) there was a small benefit of individual education on glycaemic control (WMD -0.3% (-3 mmol/mol), 95% CI -0.5 (-5) to -0.1 (-1), $p = 0.007$).

1⁺⁺

The X-PERT programme of six-weekly sessions of two hours duration has been compared with 'usual' care. Patients who took part in this programme showed a reduction in HbA1c of 0.6% (7 mmol/mol) at up to 14 months follow up ($p < 0.001$).³⁵ Body weight reduced slightly (-0.5 kg v +1.1 kg (controls) ($p < 0.001$) and waist circumference was reduced (4 cm in women; 2 cm in men) ($p < 0.001$). Sixteen per cent of patients who took part in the X-PERT programme were able to reduce their diabetes medication. Lifestyle outcomes were also improved with improvement in knowledge outcomes, number of days exercising and total empowerment. The X-PERT programme has been evaluated in a computer based simulation used to project long-term health benefits and cost effectiveness.⁷⁵⁹ This study showed that X-PERT was associated with a QALY gain of 0.09 and an increase in total health care costs of €718 per participant, giving an incremental cost per QALY of about €10,000, compared to 'usual' care. Sensitivity analyses suggested that there was a very high probability that the programme would be cost effective at a threshold of €20,000.

1++

The Diabetes Education and Self-Management for Ongoing and Newly Diagnosed (DESMOND) programme has been introduced for patients with type 2 diabetes. This programme did not lead to improvement in HbA1c after 12 months but was associated with around 1 kg greater weight loss and 5% less cigarette smoking. The intervention group also showed a greater understanding of diabetes and a lower prevalence of depression.²⁷

1++

The cost effectiveness of the DESMOND programme has been evaluated using the same computer based simulation model.⁷⁵⁹ This study showed that DESMOND was associated with a QALY gain of 0.01 and an increase in health care costs of €63 per participant, with an incremental cost per QALY of about €32,000, compared to 'usual' care. Sensitivity analyses suggested that there was a 10% probability that the programme would be cost effective at a threshold of €20,000. The cost effectiveness study notes that the DESMOND trial provided enhanced standard care to control subjects and this may result in an underestimation of its effects in relation to the other programmes.⁷⁵⁹

A **Adults with type 2 diabetes should have access to structured education programmes based upon adult learning theories.**

3.3 SELF MONITORING OF GLYCAEMIA

Self monitoring of glycaemia is a commonly used strategy for people with type 1 and type 2 diabetes to manage glycaemic control. Self monitoring of blood glucose (SMBG) is accepted standard practice for people with type 1 diabetes. Self monitoring of blood glucose for people with type 2 diabetes can guide adjustment of insulin or other medication for patients and health professionals as part of a comprehensive package of diabetes care, encourage self-empowerment and promote better self-management behaviours. Conversely self monitoring may fail to improve diabetes control and has been associated with negative psychological outcomes.^{36, 37} Other methods of self monitoring include self monitoring of urine glucose (SMUG) and measurement of blood or urine ketones. Continuous monitoring of interstitial glucose (CMG) is an alternative for people with type 1 diabetes who have persistent problems with glycaemic control.

1++

3.3.1 SELF MONITORING OF BLOOD GLUCOSE IN PEOPLE WITH TYPE 1 DIABETES

Self monitoring of blood glucose is a fundamental and established component of self-management in people with type 1 diabetes and evidence for its routine use has not been reviewed.

One systematic review identified poor quality studies which assessed the effect of frequency of self monitoring on glycaemia in people with type 1 diabetes.³⁸ One non-randomised trial in children and two observational studies in adults reported that more frequent blood glucose monitoring (≥ 3 tests per day) was associated with improvements in glycaemia. However, one small crossover study in adults with type 1 diabetes reported that there was no difference in HbA1c between those who tested twice each day for a week compared with those who tested four times daily on two non-consecutive days per week.

2++

The importance of SMBG whilst driving should be reinforced in people with type 1 diabetes.

Continuous glucose monitoring

Although SMBG is a vital part of the management of glycaemia in people with type 1 diabetes, many patients do not routinely monitor glucose levels either postprandially or overnight, which may leave undetected episodes of hyperglycaemia and hypoglycaemia respectively.³⁹ Systems using continuous monitoring of glucose by means of subcutaneous sensors which measure interstitial glucose levels have been developed. These systems are generally only considered for use by patients who experience particular difficulties in maintaining normal glucose levels or who have been transferred to continuous subcutaneous insulin infusion therapy (see section 5.3.2).

2+

The evidence on the value of CGM in people with type 1 diabetes is conflicting.

One RCT demonstrated a reduction in HbA1c at three months of 1.0% (11 mmol/mol) \pm 1.1% (12 mmol/mol) (CGM group) v. 0.4% (4 mmol/mol) \pm 1.0% (11 mmol/mol) (conventional SMBG group) ($p=0.003$) in both adults and children with poorly controlled type 1 diabetes (HbA1c > 8.1% (65 mmol/mol)).⁴⁰

1+

Another RCT in adults and children with type 1 diabetes and excellent glycaemic control (HbA1c < 7.0% (53 mmol/mol)) reported that subjects using CGM maintained HbA1c levels over six months without a corresponding rise in hypoglycaemia, (baseline 6.4% (46 mmol/mol) \pm 0.5 (5 mmol/mol) at baseline with 0.02% (0.2 mmol/mol) \pm 0.45 (5 mmol/mol) increase at six months). People in the control group using conventional SMBG reported a significant increase in HbA1c over the same period (treatment group difference -0.34% (3.72 mmol/mol), 95% CI -0.49 (-5.36) to -0.20 (-2.19), $p < 0.001$).⁴¹

1+

In contrast, a large RCT including adults with type 1 and type 2 diabetes using insulin showed no significant differences in HbA1c between people using CGM or standard SMBG, or between baseline HbA1c and follow-up measurement at 3, 6, 12 or 18 months. No significant differences were found between the groups in the number of hypo- and hyperglycaemic events. This study also reported that CGM was not cost effective.⁴²

1++

One RCT of adults and children with poorly controlled type 1 diabetes (HbA1c 7.0 to 10.0% (53 to 86 mmol/mol)) assigned patients to CGM or SMBG and stratified results according to age. The only significant reduction in HbA1c was reported in the group aged 25 years or older using CGM compared with those using SMBG (mean difference in change, -0.53% (-5.79 mmol/mol), 95% CI -0.71 (-7.76) to -0.35 (-3.83), $p < 0.001$). The between-group difference was not significant among those who were 15 to 24 years of age (mean difference, 0.08% (1.87 mmol/mol), 95% CI, -0.17 (-1.86) to 0.33 (3.61), $p = 0.52$) or among those who were 8 to 14 years of age (mean difference, -0.13% (-1.42 mmol/mol), 95% CI, -0.38 (-4.15) to 0.11 (1.20), $p = 0.29$).⁴³

1+

One systematic review of five poor quality RCTs on CGM versus SMBG in children with type 1 diabetes showed no additional benefit for CGM on HbA1c results.⁴⁴

1+

CGM may be a useful adjuvant to conventional self monitoring in selected adults with type 1 diabetes as an aid to improve glycaemic control, however further research is required to identify the groups of patients who will gain most benefit.

- CGM should not be used routinely in people with diabetes.

3.3.2 SELF MONITORING OF BLOOD GLUCOSE IN PEOPLE WITH TYPE 2 DIABETES

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.⁴⁵

The evidence for the benefit of self monitoring of blood glucose in people with type 2 diabetes is conflicting. One large RCT found no significant effect of SMBG on HbA1c between groups randomised to standard care (no self monitoring), less intensive self monitoring with clinician interpretation of results and more intensive self monitoring with self interpretation of results.³⁶ The study reported a negative impact of SMBG on quality of life, and economic analysis indicated it was associated with higher healthcare costs and was not cost effective if used routinely (average additional annual cost per patient of £92 (95% CI, £80 to £103) in the less intensive group and £84 (95% CI £73 to £96) in the more intensive group).

1++

One systematic review of studies in patients with type 2 diabetes who did not use insulin showed benefit for SMBG in reducing HbA1c levels in six of 11 trials included. Of the remaining five studies, two were underpowered, two compared SMBG against urine monitoring and one had an unusual three-armed design. ⁴⁶	1++
A comprehensive systematic review investigated the effect of SMBG on glycaemia, micro- and macrovascular disease and other diabetes outcomes in people with type 2 diabetes. ³⁸ It identified three non-randomised studies of poor quality, including people with type 2 diabetes on insulin, which reported statistically significant reductions in HbA1c ranging from -0.36% (-3.93 mmol/mol) (95% CI -0.24 (-2.62) to -0.48 (-5.25)) to -1.00% (-10.93 mmol/mol) (95% CI -1.68 (-18.36) to -0.32 (-3.50)).	2++
Only one poor quality non-randomised study was cited in this review which reported the effect of SMBG on hypoglycaemia in people with type 2 diabetes using insulin. ⁴⁷ Hypoglycaemia was reduced in people monitoring glucose four times daily once per week (RR 0.45, 95% CI 0.03 to 6.86) and four times daily once per two weeks (RR 0.67, 95% CI 0.04 to 10.11) compared with those who did not monitor glucose. Rates of hypoglycaemia, however, were very low overall and the study only followed up patients for 12 weeks.	2-
For people with type 2 diabetes not treated with insulin a meta-analysis of seven RCTs showed a clinically small but statistically significant reduction in HbA1c in favour of those using SMBG (WMD -0.25% (-2.73 mmol/mol), 95% CI -0.36 (-3.93) to -0.15 (-1.64)). ³⁸ Those using SMBG more than twice daily achieved a larger reduction in HbA1c compared with those testing less frequently (WMD -0.47% (-5.14 mmol/mol), 95% CI -0.79 (-8.63) to -0.15 (-1.64)). Subgroup analysis showed larger improvements in glycaemia with SMBG in patients with baseline HbA1c levels of 8.0% (64 mmol/mol) or above (WMD -0.30% (-3.28 mmol/mol), 95% CI -0.54 (-5.90) to -0.17 (-1.86)) compared with patients with baseline level less than 8.0% (64 mmol/mol) (mean difference -0.16% (-1.75 mmol/mol), 95% CI -0.34 (-3.72) to 0.03 (0.33)).	1++
Two further meta-analyses reported a reduction in HbA1c of 0.4% using SMBG for people with type 2 diabetes who are not using insulin. ^{48,49}	1++
One meta-analysis included three RCTs which reported that the relative risk of overall hypoglycaemia was greater with SMBG compared with no SMBG (1.99, 95% CI 1.37 to 2.89), however the rate of overall hypoglycaemia in patients using SBMG was lower (rate ratio 0.73, 95% CI 0.55 to 0.98). ³⁸ The authors speculate that this may be accounted for by the fact that increased detection of hypoglycaemia in those initiating SMBG (which results in a higher risk of overall hypoglycaemia) may produce behaviour changes that reduce future hypoglycaemic events, resulting in a lower rate of overall hypoglycaemia.	1++
One RCT involving 610 patients with type 2 diabetes using the sulphonylurea gliclazide reported that although the total number of hypoglycaemic episodes was similar in the SBMG and non-SMBG groups there was a more than twofold increase in incidence of symptomatic hypoglycaemic events in the non-SMBG group (64 symptomatic episodes of hypoglycaemia out of 66 total hypoglycaemic episodes compared with 27/51 in the SMBG group). ⁵⁰ This suggests that patients taking sulphonylureas may gain benefit from SMBG in terms of ability to pre-empt episodes of symptomatic hypoglycaemia, however the study was not designed to show this categorically.	1+
No significant differences were reported in rates of macrovascular disease, body weight, patient well-being or patient satisfaction in people using SBMG. ^{36,38,51}	1++
The impact of SBMG on management of glycaemic control is positive but small for patients with type 2 diabetes who are not on insulin, and slightly larger, but based on poorer evidence, for those using insulin. It is difficult to use the evidence base to define those patients with type 2 diabetes who will gain most benefit from SBGM. Extrapolation from the evidence would suggest that specific subgroups of patients may benefit. These include those who are at increased risk of hypoglycaemia or its consequences, and those who are supported by health professionals in acting on glucose readings to change health behaviours including appropriate alterations in insulin dose. Further research is needed to define more clearly which subgroups are most likely to benefit.	

B **SMBG is recommended for patients with type 1 or type 2 diabetes who are using insulin where patients have been educated in appropriate alterations in insulin dose.**

B **Routine self monitoring of blood glucose in people with type 2 diabetes who are using oral glucose-lowering drugs (with the exception of sulphonylureas) is not recommended.**

Motivated patients with type 2 diabetes who are using sulphonylureas may benefit from routine use of SMBG to reduce risk of hypoglycaemia.

SMBG may be considered in the following groups of people with type 2 diabetes who are not using insulin:

- those at increased risk of hypoglycaemia
- those experiencing acute illness
- those undergoing significant changes in pharmacotherapy or fasting, for example, during Ramadan
- those with unstable or poor glycaemic control (HbA1c > 8.0% (64 mmol/mol))
- those who are pregnant or planning pregnancy.

3.3.3 URINE GLUCOSE MONITORING IN PEOPLE WITH TYPE 2 DIABETES

One meta-analysis⁴⁸ and two systematic reviews^{51,52} were identified. Studies suggest that urine testing is equivalent to blood testing but these studies were generally carried out in an era when HbA1c levels were higher than would now be considered acceptable, limiting the applicability of these data to current practice.

The meta-analysis suggests that a very modest improvement in glycaemic control is associated with urine testing versus placebo (HbA1c -0.14% (-1.53 mmol/mol)), which is unlikely to be of clinical importance.⁴⁸ There is no evidence describing an impact of urine monitoring on rates of hospital admission, rates of diabetic ketoacidosis (DKA), or mortality.

1+

B **Routine self monitoring of urine glucose is not recommended in patients with type 2 diabetes.**

3.3.4 BLOOD AND URINE KETONE MONITORING

Ketone monitoring using urine, or more recently blood, is generally accepted practice in type 1 diabetes. Detection of ketones can assist with insulin adjustment during illness or sustained hyperglycaemia to prevent or detect DKA. It is not however recommended as a routine measurement.

One small RCT and a cross-sectional study assessed the benefits of blood ketone monitoring against urine ketone monitoring in a range of settings.

The RCT reported hospital attendance and emergency complications were reduced (60% fewer hospitalisations and 40% fewer emergency assessments) with an overall 50% reduction in need for hospitalisation ($p=0.05$) when comparing blood glucose with urine ketone monitoring in adolescent patients with type 1 diabetes.⁵³ The event rates in the trial were small.

1+

In the emergency department setting, a cross-sectional study suggested that blood ketone measurement may be a more accurate predictor of ketosis/acidosis than urine ketone measurement.⁵⁴ Sensitivity and specificity for the measurement of hyperketonemia from blood capillary samples were 91% and 56% respectively and were 82% and 54% from urine samples respectively.

2+

There is insufficient evidence to make a recommendation on the routine measurement of ketones in patients with type 1 or type 2 diabetes.

When ketone monitoring is required during sustained hyperglycaemia, blood ketone monitoring with increased healthcare professional support is preferable to urine ketone monitoring in young adults with type 1 diabetes.

3.4 SMOKING CESSATION

3.4.1 RISKS ASSOCIATED WITH SMOKING

In the general population tobacco smoking is strongly and dose-dependently associated with all cardiovascular events, including coronary heart disease (CHD), stroke, peripheral arterial disease (PAD) and cardiovascular death.^{55, 56} In people with diabetes smoking is an independent risk factor for cardiovascular disease⁵⁷⁻⁵⁹ and the excess risk attributable to smoking is more than additive.⁶⁰ Smoking cessation reduces these risks substantially, although the decrease is dependent on the duration of cessation.^{61, 62} Men who smoke are three times more likely to die aged 45-64 years, and twice as likely to die aged 65-84 years than non-smokers.⁵⁵ Studies done among women during the 1950s and 1960s reported relative risks for total mortality ranging from 1.3 to 1.4. Smokers in the Nurses' Health Study were at nearly 1.9 times the risk compared with people who have never smoked.

2++
4

For microvascular disease the evidence is less clear. A good quality Swedish case control study provides supportive evidence for current or former history of smoking (at five years before survey) as a significant risk factor for chronic kidney disease (CKD) in a community based population.⁶³ Odds ratios (OR) increased with increasing frequency and duration of smoking. A 'pack year' is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years an individual has smoked. More than 15 pack years of smoking increased the risk of CKD significantly (16-30 pack years, OR 1.32; > 30 pack years, OR 1.52).

2+

There is a suggestion that smoking may be a risk factor for retinopathy in type 1 diabetes^{64, 65} but not in people with type 2 diabetes.^{66, 67}

2+

In the Scottish Diabetes Survey 2009 nearly 1 in 5 people with diabetes were recorded as being current smokers, which is slightly lower than among the general population.¹

B All people who smoke should be advised to stop and offered support to help facilitate this in order to minimise cardiovascular and general health risks.

3.4.2 FIRST LINE INTERVENTIONS

Studies in patients with diabetes support the use of intensive management in the form of motivational interviewing or counselling in combination with pharmacological therapies such as bupropion and nicotine replacement. Two RCTs (280 and 368 patients) compared intensive versus conventional management and demonstrated increased quit rates from 2.3% to 17% and 14% to 40% respectively.^{68, 69} A smaller study of 60 patients involving intensive management without the addition of pharmacological treatment demonstrated a positive trend for quit rates at three months but a non-significant result at six months.⁷⁰

1+
2+

Group behaviour therapy is more effective than self help material but has not been proven to be superior to individual advice.⁷¹

1++

A Healthcare professionals involved in caring for people with diabetes should advise them not to smoke.

B Intensive management plus pharmacological therapies should be offered to patients with diabetes who wish to stop smoking.

There is no clear evidence suggesting that pharmacological intervention or counselling strategies to aid smoking cessation in patients with diabetes should differ to those used in the general population. For general smoking cessation advice refer to SIGN 97 on Risk estimation and the prevention of cardiovascular disease.⁷²

4

3.4.3 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%.^{73,74}

1+

B Healthcare 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 (eg walking, gardening, stair climbing).

Health-enhancing physical activity is physical activity conducted at a sufficient level to bring about measureable health improvements. This normally equates to a moderate intensity level or above and can generally be described as activity that slightly raises heart rate, breathing rate and core temperature but in which the patient is still able to hold a conversation.

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

3.5.2 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.⁷⁵ 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. A rate of perceived exertion scale is useful for estimating exercise intensity, particularly in people with autonomic neuropathy who have reduced maximal heart rate.⁷⁶

4

3.5.3 EFFECTS OF PHYSICAL ACTIVITY AND EXERCISE 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 a minimum of four years.⁷⁷⁻⁸³

2+

2++

Several randomised trials have determined the effects of lifestyle interventions, including physical activity and exercise, on the progression from IGT to diabetes over a period ranging from three to six years. All of these studies have shown a relative risk reduction varying from 46 to 58% in the development of type 2 diabetes.⁸⁴⁻⁸⁷

1++

1+

B All people should be advised to increase their level of physical activity to achieve current physical activity recommendations and be supported to maintain this level across the lifespan.

3.5.4 EFFECTS OF PHYSICAL ACTIVITY AND EXERCISE ON THE MANAGEMENT OF DIABETES

Both structured, supervised exercise programmes and less structured, unsupervised physical activity programmes (of variable activity type and mode of delivery) are effective for improving glycaemic control and cardiovascular risk factors in people with type 2 diabetes. Programmes lasting from eight weeks to one year improve glycaemic control as indicated by a decrease in HbA1c levels of 0.6% (7 mmol/mol), 95% CI 0.9 (9.84) to 0.3 (3.28), $p < 0.05$.⁸⁸ The exercise intervention significantly decreased plasma triglycerides (-0.2 mmol/l, 95% CI -0.48 to -0.02), and there was a reduction in visceral adipose tissue with exercise (-45.5 cm², 95% CI -63.8 to -27.3). No significant difference was found between groups in quality of life, plasma cholesterol or blood pressure.

A **People with type 2 diabetes should be encouraged to participate in physical activity or structured exercise to improve glycaemic control and cardiovascular risk factors.**

Limited research has addressed the economic impact of physical activity and exercise programmes.⁸⁹ There is insufficient evidence to draw a conclusion on the cost effectiveness of structured exercise.

A systematic review of randomised and observational studies reported that exercise and physical activity programmes in people with type 1 diabetes do not improve glycaemic control but improve cardiovascular risk factors.⁹⁰ It was not possible to identify specific intervention details or effect sizes due to the heterogeneity of studies and gaps in the research.

1+

B **People with type 1 diabetes should be encouraged to participate in physical activity or structured exercise to improve cardiovascular risk factors.**

3.5.5 PRESCRIPTION OF PHYSICAL ACTIVITY AND EXERCISE FOR PEOPLE WITH DIABETES

Various guidelines exist for physical activity and exercise in the general population. The most recent guidelines from the US Department of Health and Human services (2008) recommend the following:

- Adults (aged 18–64 years) should build up to achieve a minimum of 2.5 hours each week of moderate-intensity, or 75 minutes each week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic physical activity. Aerobic activity should be performed in episodes of at least 10 minutes and preferably be spread throughout the week (ie 30 minutes of activity on at least five days of the week). Greater amounts of activity should provide greater health benefits, particularly for weight management. Adults should also do moderate- or high-intensity muscle-strengthening activities that involve all major muscle groups on two or more days per week.
- Older adults (aged 65 years and older) should follow the adult guidelines. If this is not possible due to limiting chronic conditions, older adults should be as physically active as their abilities allow. They should avoid inactivity. Older adults should also try to do exercises that maintain or improve balance if they are at risk of falling.

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 it may be easier for people with type 1 diabetes to perform physical activity or exercise every day.⁹¹

4

Aerobic, endurance exercise is usually recommended, however resistance exercise with low weights and high repetitions is also beneficial.⁹² A combination of both aerobic and resistance exercise appears to provide greater improvement in glycaemic control than either type of exercise alone.⁸⁸

1+

1++

D **Exercise and physical activity (involving aerobic and/or resistance exercise) 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.⁹³ 4

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

An evidence based public health guidance document reported that there was insufficient evidence to recommend the use of exercise referral schemes to promote physical activity other than as part of research studies where their effectiveness is being evaluated.⁹⁴ 4

One more recent RCT demonstrated an exercise referral programme, specifically tailored for people with newly diagnosed type 2 diabetes, to be effective for improving physiological parameters and mood state at 12 weeks post intervention.⁹⁵ In this study the addition of a physical activity consultation (in which cognitive behavioural skills were developed) enhanced programme attendance and adherence to physical activity at six months.

3.5.6 ADVICE FOR PATIENTS TAKING INSULIN OR GLUCOSE-LOWERING 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 will significantly reduce the risk of hypoglycaemia and delayed hypoglycaemia.⁹⁶ 2+

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

Injection of insulin into exercising areas increases the absorption of insulin and the risk of hypoglycaemia and should therefore be avoided.⁹⁶⁻⁹⁸ 2+

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.⁹⁶ 4

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.

Patients using glucose-lowering drugs, such as sulphonylureas, may also be at risk of hypoglycaemia during exercise.

3.5.7 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.⁹⁶ 4

Research demonstrates that high-intensity exercise may transiently increase albumin excretion rate (AER) in people with or without diabetes. No evidence of more rapid progression of nephropathy or retinopathy was identified in subjects with diabetes who exercise more.^{99,100} 2+

Weight-bearing physical activity and brisk walking programmes in people with type 2 diabetes and peripheral neuropathy do not increase the risk of foot ulcers.¹⁰¹ 1+

There is higher risk of myocardial infarction (MI) after heavy exertion in sedentary compared with non-sedentary people with type 1 diabetes.¹⁰² 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 with slow progressions in volume and intensity should be recommended for sedentary people with diabetes.

3.6 WEIGHT MANAGEMENT IN TYPE 2 DIABETES

Type 2 diabetes is associated with obesity (defined as body mass index $> 30 \text{ kg/m}^2$). Obesity is associated with a significant negative impact on morbidity and mortality and weight management is an integral part of diabetes care. Weight loss in obese individuals has been associated with reductions in mortality, blood pressure, lipid profiles, arthritis-related disability and other outcomes.¹⁰³ Studies have not addressed the impact of weight loss on complications of diabetes including retinopathy, nephropathy or neuropathy.

The SIGN guideline on the management of obesity provides detailed recommendations on the prevention and treatment of obesity within the clinical setting, in children, young people and adults.¹⁰³ The guideline addresses:

- diagnosis of overweight and obesity
- primary prevention of obesity
- treatment of obesity by diet, lifestyle interventions, drugs and bariatric surgery
- prevention of weight regain following treatment.

In addition, the guideline discusses the benefits of weight loss on glycaemic control in people with established diabetes and the prevention and remission of both established diabetes and impaired glucose tolerance. While a brief summary of weight loss interventions in people with diabetes is included here, the SIGN obesity guideline should be the primary resource for evidence based recommendations on management of obesity.

3.6.1 WEIGHT LOSS

One meta-analysis including 22 studies ($n = 4,659$ with follow up one to five years) demonstrated a mean weight loss of 1.7 kg (95% CI 0.3 to 3.2), or 3.1% of baseline body weight with lifestyle intervention. Within this meta-analysis, several studies reported a significant reduction in HbA1c of 1.0% to 2.6% with lifestyle intervention corresponding to weight loss.¹⁰⁴

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In one RCT weight loss of 8.5% through an intensive education and support programme decreased HbA1c by 0.64% (6.99 mmol/mol) and decreased fasting blood glucose by 1.19 mmol/l. The use of glucose-lowering medication was reduced from 86.5% to 78.6%.¹⁰⁵

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One meta-analysis of eight studies examined the effects of Very Low Energy Diets (VLED) and Low Energy Diets (LED) in 219 obese subjects with type 2 diabetes. Although the type and duration of intervention varied across the studies, subjects lost 11.1% of their initial weight and fasting plasma glucose decreased by 14.7% at 48 weeks.¹⁰⁶

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One systematic review of 14 RCTs investigated a range of different weight reducing diets and included participants with type 2 diabetes, hypertension, MI, asthma and breast cancer. Four RCTs provided data comparing a Protein Sparing Modified Fast (PSMF) with a Low Calorie Diet (LCD) and found no statistically significant differences in HbA1c or weight loss between these two interventions.¹⁰⁷

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A systematic review, including 22 studies on pharmacotherapy for weight loss in adults with type 2 diabetes, focused mainly on weight loss and HbA1c data for orlistat ($n = 2,036$ participants), sibutramine ($n = 296$) and fluoxetine ($n = 1,047$).¹⁰⁸ Orlistat resulted in a mean pooled effect weight loss of 2.0 kg (95% CI 1.3 to 2.8) associated with a reduction in HbA1c of 0.5% (5.46 mmol/mol) (95% CI 0.3 (3.28) to 0.6 (6.56)) with follow up between 24 and 57 weeks. Sibutramine resulted in mean pooled effect weight loss of 5.1 kg (95% CI 3.2 to 7.0) with no reduction in HbA1c after follow up of 12 to 52 weeks. Fluoxetine resulted in mean pooled effect weight loss of 3.4 kg (95% CI, 1.7 to 5.2) at 8 to 16 weeks, 5.1 kg (95% CI, 3.3 to 6.9) at 24 to 26 weeks and one study produced a loss of 5.8 kg (95% CI, 0.8 to 10.8) at 52 weeks with no reduction in HbA1c. Gastrointestinal side effects were common with orlistat; tremor, somnolence and sweating with fluoxetine; and palpitations with sibutramine.

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The long term benefits of weight loss on glycaemic control have not been adequately assessed.

3.6.2 BARIATRIC SURGERY

A systematic review and meta-analysis of 621 studies (including 135,246 people; mean body mass index (BMI) 47.9) investigated the effects of different kinds of bariatric surgery and considered the role of these surgical techniques upon resolution of established type 2 diabetes.¹⁰⁹ Most included studies were observational with only 4.7% being RCTs. For patients with type 2 diabetes total mean weight loss was 40.6 kg. This benefit lasted for beyond two years after intervention. Diabetes resolution was greatest for patients undergoing biliopancreatic diversion/duodenal switch (95.1% resolved); followed by gastric bypass (80.3% resolved); gastroplasty (79.7% resolved) and then laparoscopic adjustable gastric banding (56.7% resolved).

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A systematic review containing 11 studies examined the effects of long term weight loss on diabetes outcomes in people with type 2 diabetes.¹¹⁰ Two studies reported extreme weight loss following bariatric surgery.^{111,112} Ninety three per cent of patients either remitted or demonstrated an improvement in glycaemia following weight loss surgery. Similarly, 90% of patients with preoperative impaired glucose tolerance in one study had normal glucose handling following surgical intervention.¹¹¹

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In an RCT of 60 patients with a diabetes diagnosis of less than two years which was published after the systematic review, there was remission of diabetes in 73% of the group receiving adjustable gastric banding bariatric surgery compared with 15% in the control group who received a range of non-surgical treatments for obesity ($p < 0.001$).¹¹³ Surgical and control groups lost a mean of 20.0% and 1.4% body weight, respectively at two years ($p < 0.001$). Remission of diabetes was related to weight loss and lower baseline HbA1c levels. There were no serious adverse events in either group.

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In a large prospective cohort study of 1,703 obese subjects, 851 patients underwent adjustable gastric banding, vertical banded gastroplasty or gastric bypass and were matched to control subjects who received non-surgical intervention according to local protocols.¹¹⁴ At two years there was weight gain of 0.1% in the control group and weight loss of 23.4% in the surgical group ($p < 0.001$). At 10 years, the control group gained 1.6% weight and the surgical group had weight loss of 16.1% ($p < 0.001$). Recovery from diabetes and other cardiovascular risk factors was significantly more common in the surgical group than in the control group, both at two and 10 years.

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In a retrospective cohort study of 402 subjects with type 2 diabetes undergoing laparoscopic gastric banding, excess weight loss for patients with diabetes was 39.2% at one year, 46.7% at 18 months, and 52.6% at two years. Mean HbA1c decreased from 7.35% (56.8 mmol/mol) (range 5.6 (38) to 11 (97)) to 5.8% (40 mmol/mol) (range 5.0 (31) to 6.2 (44)) at two years. There was withdrawal of diabetic medications in 66% at one year and 80% at two years.¹¹⁵

2⁺

Due to the absence of head-to-head comparisons between weight loss interventions it is not possible to recommend a single approach.

A **Obese adults with type 2 diabetes should be offered individualised interventions to encourage weight loss** (including lifestyle, pharmacological or surgical interventions) **in order to improve metabolic control.**

3.7 HEALTHY EATING

3.7.1 DIETARY RECOMMENDATIONS FOR PEOPLE WITH DIABETES

Eating healthily is of fundamental importance as part of diabetes healthcare behaviour and has beneficial effects on weight, metabolic control and general well-being.^{116,117} Salt restriction in the general population is discussed in the SIGN guideline on risk estimation and the prevention of cardiovascular disease (SIGN 97).⁷²

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One meta-analysis of 11 RCTs investigated the efficacy of different diets to improve glycaemic control in people with type 1 and type 2 diabetes aged from 10 to 60 years.¹¹⁸ Pooled data for six trials measuring HbA1c showed a mean reduction of 0.5% (5.46 mmol/mol) (95% CI 0.8 (8.74) to 0.2 (2.19), $p=0.001$) for patients on low glycaemic index (GI) diets compared with higher GI diets. In two studies a low GI diet was associated with reduced reports of hypoglycaemia. The authors note that some randomisation information was inadequate and bias from unblinded assessors cannot be ruled out.

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There is insufficient evidence to make a recommendation about specific diets for improving glycaemic control.

There is no evidence on patient satisfaction, quality of life or hospital admission rates with reference to particular diets. Insufficient evidence exists to make a comparison of hyper and hypoglycaemia rates between different diets.

High dropout rates and poor compliance with carbohydrate- and energy-restricted diets demonstrated in trial settings would suggest that such diets are not widely applicable or acceptable to patients.^{119,120} Short term (six months) low carbohydrate diets containing as little as 50 g carbohydrate per day (13% of daily energy)¹²⁰ or 110 g per day (33% of daily energy)¹¹⁹ appear safe in type 2 diabetes whether treated by diet, tablets, insulin or a combination. In patients who adhere to a low carbohydrate diet a reduction in insulin and/or oral hypoglycaemic agent dose is likely to be necessary.

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B People with type 2 diabetes can be given dietary choices for achieving weight loss that may also improve glycaemic control. Options include simple caloric restriction, reducing fat intake, consumption of carbohydrates with low rather than high glycaemic index, and restricting the total amount of dietary carbohydrate (a minimum of 50 g per day appears safe for up to six months).

In patients with type 2 diabetes, a systematic review of short term supplementation with omega-3 polyunsaturated fatty acid (PUFA) showed a reduction in triglycerides (TG) but a rise in low density lipoprotein (LDL) cholesterol.¹²¹

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B Dietary supplementation with omega-3 PUFA is not generally recommended in people with type 2 diabetes.

Supplementation with 500 mg tocopherol (vitamin E) per day for six weeks in patients with well controlled type 2 diabetes caused increased heart rate and blood pressure.¹²²

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B Vitamin E supplementation 500 mg per day is not recommended in people with type 2 diabetes.

3.7.2 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. 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.⁸⁴ However, other studies have demonstrated that if people who are overweight lose weight, by whatever method, their risk of developing diabetes is reduced.^{83,116,123-125}

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B Overweight individuals and those at high risk of developing diabetes should be encouraged to reduce this risk by lifestyle changes including weight management and physical activity.

3.7.3 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, HbA1c, lipids, and self care behaviour for up to two years after the initial intervention.¹²⁶⁻¹³² However, it is not always possible to identify if the benefit is wholly attributable to the intervention, or dependent on how or where the care is delivered.

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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.¹³³⁻¹³⁷ 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.¹³⁸⁻¹⁴¹

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

3.8 ALCOHOL

Alcohol is known to have both beneficial and harmful effects on the biochemical basis of CHD and the psychological consequences of the disease.¹⁴²

Consuming over 40 g/day alcohol increases a man's risk of liver disease, raised blood pressure and some cancers (for which smoking is a confounding factor) and violent death. For women consuming more than 24 g/day average alcohol increases their risk of developing liver disease and breast cancer.¹⁴³

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3.8.1 EFFECT OF ALCOHOL ON CARDIOVASCULAR RISK

Observational evidence suggests a protective effect of alcohol consumption for vascular endpoints including death in patients with type 2 diabetes.¹⁴⁴⁻¹⁴⁶ Studies that have stratified alcohol intake describe the familiar 'J' shaped curve relating alcohol consumption and a measure of vascular risk in patients with type 2 diabetes. One case control study¹⁴⁴ suggests that the threshold for increased risk of admission to hospital with an acute coronary syndrome occurs at a lower level of alcohol consumption (one glass of wine or 12 g daily, OR 0.53, 95% CI 0.28 to 0.97) than that found in the general population.

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B People with diabetes can take alcohol in moderation as part of a healthy lifestyle but should aim to keep within the target consumption recommended for people without diabetes.

3.8.2 EFFECT OF ALCOHOL ON GLYCAEMIA

There is evidence that drinking 2-3 units of alcohol is not associated with hypoglycaemia in people with type 1 or type 2 diabetes.¹⁴⁷⁻¹⁵²

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However, acute alcohol consumption reduces hypoglycaemia awareness. Both acute alcohol consumption and acute hypoglycaemia adversely affect cognitive function and their effects are additive.¹⁵³

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

3.8.3 EFFECT OF ALCOHOL ON COMPLICATIONS OF DIABETES

There is insufficient evidence to determine if risk or severity of other diabetes complications is affected by alcohol consumption.¹⁴⁵

3.9 CHECKLIST FOR PROVISION OF INFORMATION

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

Healthcare professionals should:

- explain the health risks associated with smoking and encourage patients to quit. They should inform the patient of the range of smoking cessation services available (see *SIGN 97*) and facilitate referral to local services if appropriate.
- involve carers and family members in diabetes education and care to encourage family support and understanding.
- offer individualised interventions to people with diabetes to help promote weight loss, where necessary.

People with diabetes should:

- speak to their family members about their diabetes to encourage diabetes awareness to help prevent development of type 2 diabetes in their first degree relatives by lifestyle modification.
- increase their levels of physical activity in line with current physical activity recommendations. Some people might find structured exercise classes useful in this regard.
- increase physical activity levels gradually where starting levels are low.
- seek professional advice before embarking on an exercise programme if they have existing complications of diabetes or other medical problems.
- understand and follow healthy eating recommendations. This should include calorie restriction where weight loss is desirable.

4 Psychosocial factors

Studies investigating the relationships among psychological and social variables and diabetes outcomes are generally cross-sectional in nature, rather than longitudinal, and often fail to report pre-diagnosis baseline data. Furthermore, researchers use different terms to describe the foci of their studies yet measure the same outcome. For example, studies investigating self management, adherence, and diabetes control all typically use HbA1c as the primary outcome measure, which is appropriate because self-management and adherence are mediators of diabetes control. These different ways of describing diabetes outcomes are included in the literature.

Similarly, researchers use a wide variety of psychological terms to describe human behaviour and the nature of psychological interventions even when detailing broadly the same things. For example, some investigators of children with type 1 diabetes who are finding life and control difficult report childhood behavioural problems, some detail parenting problems, and others highlight family dysfunction. These descriptions commonly reflect the theoretical position of researchers rather than substantial differences in reported behaviour.

Research on the efficacy of psychological interventions in diabetes is in its infancy. Most outcomes have been reported over relatively short periods considering diabetes is a lifelong condition and conclusions about using these interventions on ethnic minorities may be problematic because of their lack of representation in the research. In most intervention studies reviewed, patients are recruited into trials from diabetes clinics, are not newly diagnosed and do not have significant comorbid medical problems. Some trials recruit only patients with poorly controlled diabetes,^{154,155} whereas others have wider inclusion criteria.^{10,156}

Interventions reviewed include behaviour modification, motivational interviewing (MotI), cognitive behavioural therapy (CBT), acceptance and commitment therapy (ACT), goal setting, guided self-determination (GSD) and coping skills. These interventions are generally acceptable to patients, increase patient satisfaction with treatment, and apply across the spectrum of children, adolescents, and adults with type 1 and type 2 diabetes, including those whose diabetes is poorly controlled.

4.1 THE INFLUENCE OF PSYCHOSOCIAL FACTORS ON DIABETES CONTROL

There is evidence that a range of psychological and social factors can impact on the ability of people with diabetes to manage their condition. Whether the burden of managing diabetes causes psychological and social problems or vice versa, however, is unclear.

The following factors are associated with poorer control in children and young people with type 1 diabetes:¹⁵⁷

- aspects of family functioning including conflict; lack of cohesiveness and lack of openness
- depression
- anxiety
- maternal distress
- eating disorders
- behavioural problems.

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The following factors are associated with poorer control in adults with type 1 diabetes:¹⁵⁸

- clinical depression and subclinical levels of mood disruption
- anxiety
- eating disorders.

4

Depression is more common in people with diabetes than in the general population.¹⁵⁹⁻¹⁶¹ The presence of microvascular and macrovascular complications is associated with a higher prevalence of depression and lower quality of life.¹⁶²⁻¹⁶⁴ Remission of depression is often associated with an improvement in glycaemic control.^{161,164}

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B Regular assessment of a broad range of psychological and behavioural problems in children and adults with type 1 diabetes is recommended.

- In children this should include eating disorders, behavioural, emotional and family functioning problems.
- In adults this should include anxiety, depression and eating disorders.

4.2 SCREENING FOR PSYCHOLOGICAL DISTRESS

One evidence based guideline has indicated the need for health professionals working in diabetes to have sufficient levels of consulting skills to be able to identify psychological problems, or at least to the extent to be able to decide whether or not referral to specialist services is required.¹⁵⁸

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- Health professionals working in diabetes should have sufficient levels of consulting skills to be able to identify psychological problems and be able to decide whether or not referral to specialist services is required.

Depression can be assessed using simple questions regarding mood and enjoyment of day to day activities (QOF questions), using self-completed measures or via a more intensive clinical interview (normally carried out by psychologists/psychiatrists). There are some screening tools which have been validated and are widely used with the general population and with those who have medical conditions.

The performance of some self report screening tools has been assessed in people with type 1 and type 2 diabetes. These include the Beck Depression Inventory (BDI),¹⁶⁵ the Centre for Epidemiological Studies–Depression Scale (CES-D)¹⁶⁶ and the Patient Health Questionnaire (PHQ-9).¹⁶⁷ These are relatively short (21,20, 9 items respectively) and could be completed by most patients in a clinic setting within 10-15 minutes.

It is worth noting that some symptoms of diabetes overlap with symptoms of common psychological problems. On one hand this can make identification of psychological problems more difficult than is usually the case, and on the other hand this can lead to false positives when using screening tools designed for use with the general population.

The Hospital Anxiety and Depression Scale (HADS)¹⁶⁸ is the most widely used self report screening tool for adults with medical conditions, including diabetes in the UK, although there is no good quality evidence establishing reliability and validity in a diabetic population. The HADS is short (14 items) and screens for both anxiety and depression. The HADS controls for symptom overlap. An expert panel recommended the use of the HADS with adults who have diabetes in Scotland.¹⁶⁹

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There is no equivalent inventory for children.

There are also reliable validated measures of general psychological distress in relation to diabetes, including the PAID (Problem Areas in Diabetes) scale and the WHO-5 Well-being Index.¹⁷⁰ No evidence was identified for validated tools to screen for anxiety or eating disorders in people with diabetes.

There is no evidence assessing how to assess psychological problems reliably and validly in young people or adults with diabetes. In the absence of this evidence there are screening tools which have been validated and are widely used with the general population and with those who have medical conditions.

- ☑ Validated screening tools which are widely used to assess general psychological distress in the general population (eg HADS) may be used in adults or young people with diabetes.
- ☑ Healthcare professionals should be aware of cultural differences in type/presentation of psychological problems within Black and minority ethnic communities living with diabetes and facilitate appropriate psychological/emotional support.

4.3 THE EFFECT OF PSYCHOLOGICAL INTERVENTIONS ON DIABETES OUTCOMES

4.3.1 CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES

A systematic review of the literature on the effectiveness of psychoeducational interventions for adolescents reported a pooled median effect size (ES) of -0.18 on HbA1c and of -0.37 on psychological well-being.¹⁷¹ This review highlighted a number of methodological problems with the existing literature such as a lack of RCTs and a lack of clarity in the descriptions of the psychological interventions. In 2006, the review was updated and reported improvements in the quality of the literature, for example, an increased proportion of RCTs (54% v 40%) and a larger mean number of participants in newly identified studies (79.7 v 53.8 people).¹⁶ The median effect size for HbA1c (-0.17) and psychological well-being (-0.37) remained similar to that reported by the earlier review. These effect sizes for HbA1c translate to a change of about 0.3% (3 mmol/mol) and the review concludes that interventions have only a small effect on glycaemic outcomes but a more substantial effect on psychosocial function.¹⁶

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There is only one systematic review of studies that has evaluated the effects of psychological interventions on children and adolescents with diabetes whilst excluding studies of educational interventions.¹⁵⁹ This review described improvements in HbA1c of 0.48% (5.25 mmol/mol) (95% CI 0.05 (0.55) to 0.91 (9.95)) and a statistically significant reduction in psychological distress (ES -0.48, 95% CI -0.10 to -0.83). It should be noted that this effect size is smaller than is represented in the general literature on treatments for distress, however most patients in the studies included in the systematic review were not distressed at baseline.

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A further systematic review of family interventions (including educational and psychological components) on children and adolescents reported a slightly larger improvement in HbA1c (0.6% (6.56 mmol/mol)).¹⁷²

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Recent RCTs not included in these reviews have found improvements in HbA1c of 0.5% (5.46 mmol/mol) for interventions in adolescents using motivational interviewing,^{10,156} and 0.8% (8.74 mmol/mol) using goal reinforcement via text messaging.¹⁰

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4.3.2 ADULTS WITH TYPE 1 DIABETES

In adults, a systematic review evaluated the effects of psychological interventions and reported a reduction in mean HbA1c of -0.22% (2.40 mmol/mol) (95% CI 0.13 (1.42) to -0.56 (-6.12)) but no statistically significant reduction in distress (ES -0.25, 95% CI 0.01 to -0.51).¹⁵⁹ One subsequent large UK based RCT using a combination of CBT and motivational interviewing reported 12 month post-treatment results on HbA1c (a reduction of 0.46% (5.03 mmol/mol)) similar to that described above for children and young people, and considerably larger than that previously reported in meta-analysis in adults.¹⁵⁴ This trial also reported a non-significant change in depression scores at 12 month follow up although the aim was to improve glycaemic control, not psychological distress, and few of the subjects were clinically distressed.

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Compared to the general literature on psychological interventions for psychological distress, the effect sizes reported for studies of adults, adolescents and children with diabetes are low probably reflecting homogeneity of study samples (in terms of psychological distress). That is, studies did not target people with diabetes who were experiencing clinical levels of psychological problems and therefore significant reductions in this area were unlikely.

4.3.3 ADULTS WITH TYPE 2 DIABETES

One systematic review evaluated the impact of psychological interventions (including group or individual CBT or counselling) on glycaemic control in people with type 2 diabetes.¹⁷³ It showed a reduction of 0.76% (8.31 mmol/mol) in HbA1c (95% CI 0.18 (1.97) to 1.34 (14.64)), and a statistically significant reduction in psychological distress (ES -0.58, 95% CI -0.95 to -0.20), but no impact on weight control.

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A small number of RCTs show a positive impact of psychological interventions on mediators of control in people with type 2 diabetes, with small to medium effect sizes. Outcomes include self-management,¹⁷⁴ adherence,^{175,176} and lifestyle factors (walking, weight loss).^{175, 176} However it is difficult to synthesise the evidence as behavioural outcomes are often not clearly defined or comparable across studies.

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A Children and adults with type 1 and type 2 diabetes should be offered psychological interventions (including motivational interviewing, goal setting skills and CBT) to improve glycaemic control in the short and medium term.

4.4 TREATMENT OF PSYCHOLOGICAL DISTRESS

4.4.1 INTRODUCTION

There has been little research on how best to treat clinically significant psychological problems in children and adults with diabetes. As well as inevitably limiting guidance in this area, the lack of empirical evidence also means that it is unclear whether or not people with diabetes need to receive treatments that are dissimilar to those received by people without diabetes.

No evidence was identified on how to treat emotional and behavioural problems in children and young people with diabetes.

4.4.2 TREATMENT OF DEPRESSION

Antidepressant therapy with a selective serotonin reuptake inhibitor (SSRI) is a useful treatment in depressed patients with diabetes and may improve glycaemic control,¹⁷⁷ however tricyclic antidepressants may adversely affect metabolic control.¹⁷⁸

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Continued antidepressant treatment for one year after recovery may prevent recurrence of depression in some patients with diabetes.¹⁷⁹

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Cognitive behavioural therapy 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.¹⁸⁰⁻¹⁸² However, cognitive behavioural therapy may be less effective in patients with complications.¹⁶⁴

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In view of the limited evidence, the most sensible approach is for healthcare professionals who are involved in the treatment of significant psychological problems in children and adults with diabetes to refer to standard guidelines for those specific disorders.

Healthcare professionals working with adults and children with diabetes should refer those with significant psychological problems to services or colleagues with expertise in this area.

4.5 CHECKLIST FOR PROVISION OF INFORMATION

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

Healthcare professionals should:

- on those occasions where significant psychosocial problems are identified, explain the link between these and poorer diabetes control. If possible, it is good practice to also give suitable leaflets. They should advise patients where best to obtain further help, and facilitate this if appropriate.
- be mindful of the burden caused by psychosocial problems (such as clinical and sub-clinical levels of depression) when setting goals and adjusting complex treatment regimens (typically adults and children will be less able to make substantial changes to their lives during difficult times).

People with diabetes (or parents/guardians) should:

- try to speak to their general practitioner or diabetes team if they feel they (or their children) have significant psychosocial issues such as those detailed in this section.
- be mindful that many psychosocial problems make diabetes self-care harder, and also that many difficulties can be successfully treated with the right help.

5 Management of type 1 diabetes

The following recommendations are for all health professionals who advise and support people with type 1 diabetes and their families. They should be used in combination with other recent practice guidance, particularly from NICE^{157,158} and the International Society for Paediatric and Adolescent Diabetes. www.ispad.org

SIGN 55, which this guideline supersedes, contained a section on the management of type 1 diabetes in children and adolescents under the age of 16 years. Sections 5.1, 5.2, 5.3.3 and 5.5 (diagnosis, initiating therapy, dietary management and long term complications and screening) have not been significantly updated in the present review and therefore continue to relate to people aged under 16 years. The remainder of the section includes updated material which is relevant to the management of children, adolescents and adults with type 1 diabetes.

5.1 DIAGNOSIS AND EPIDEMIOLOGY

Diabetes is the most common metabolic disease in the young. In 2009 the Scottish Diabetes Survey indicated there were 27,363 patients with type 1 diabetes in Scotland.¹ The Scottish Study Group for the Care of Diabetes in the Young has shown that currently there are nearly 1,900 people aged under 15 years with diabetes in Scotland, with an annual incidence of 35 per 100,000 population by 2003, and a near quadrupling of new cases in the last 40 years (*Personal communication, Prof Norman Waugh*). The incidence in Scotland is one of the highest in the world.¹⁸³ 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.¹⁸⁴

5.1.1 SCREENING FOR TYPE 1 DIABETES

Twelve to fifteen per cent of young people under the age of 15 years with diabetes mellitus have an affected first degree relative (a positive family history).¹⁸⁵ The children of fathers with diabetes are three times more likely to develop diabetes than those of mothers with diabetes.¹⁸⁶ While there are known antibody markers of prediction in high risk subjects, there is no evidence for effective methods of prevention of type 1 diabetes.¹⁸⁷

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

5.2 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.¹⁸⁸ Management in the community using a home based education programme for patients with newly diagnosed diabetes has been shown also to be cost effective.¹⁸⁹

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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 the intensification of therapy in the attempt to achieve as rapid as possible normoglycaemia 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.

5.3 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.

5.3.1 GLYCAEMIC TARGETS

Despite compelling evidence that improved glycaemic control reduces risks of microvascular and macrovascular complications in people with type 1 diabetes⁶ no evidence was identified on outcomes associated with treatment to specific targets. Thus, there is no agreed single target for glycaemic control in these patients. Targets recommended by different authorities vary between 6.5-7.5% (48-58 mmol/mol).^{158,190,191} Targets can also vary within an individual even over a very short period of time depending on a variety of clinical and non-clinical circumstances.

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The guideline development group concluded that identifying a single target for all people with type 1 diabetes was not appropriate, but that patients should discuss this with their healthcare professionals, in the knowledge that the overall aim is to achieve the lowest HbA1c as possible, which does not interfere with the patient's quality of life.

5.3.2 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.¹⁸⁵ Limited data support an improvement in glycaemic control using three rather than two injections per day.^{185,192,193}

Evidence regarding the impact of an intensive insulin regimen upon long term control is derived principally from the Diabetes Control and Complication Trial (DCCT) which also involved a comprehensive patient support element (diet and exercise plans, monthly visits to the healthcare team etc).^{6,194} 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.

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- 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 healthcare strategies.

Both basal (eg, glargine and detemir) and rapid-acting (eg, lispro, aspart and glulisine) insulin analogues are prescribed widely in the management of type 1 diabetes.

Rapid-acting insulin analogues in adults

In comparison with regular human insulin and as part of a basal bolus regimen, short-acting insulin analogues have a small but statistically significant effect on HbA1c in people with type 1 diabetes, with a reduction of approximately 0.1%.^{195,196} In the context of long term glycaemic control this is unlikely to be clinically significant. Some studies have reported a reduction in hypoglycaemia in association with their use, however there is considerable heterogeneity between these studies, making it difficult to draw firm conclusions. The use of insulin analogues has been associated with an improvement in treatment satisfaction scores in several, though not all, studies which used a validated assessment tool.

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- B** An intensified treatment regimen for adults with type 1 diabetes should include either regular human or rapid-acting insulin analogues.

Basal insulin analogues in adults

Two meta-analyses have compared basal insulin analogues (glargine and detemir) and neutral protamine Hagedorm (NPH) insulin in adults with type 1 diabetes.

The first meta-analysis, undertaken by the Canadian Agency for Drugs and Technologies in Health, concluded that use of glargine was associated with a reduction in HbA1c of 0.11% (1.20 mmol/mol) (95% CI 0.02 (0.22) to 0.21 (2.30)) while use of detemir was associated with a reduction in HbA1c of 0.06% (0.66 mmol/mol) (95% CI -0.13 (-1.42) to +0.02 (0.22)).¹⁹⁷

Benefits in terms of hypoglycaemia were inconsistent. When glargine was compared with NPH insulin, there was no significant reduction in severe or nocturnal hypoglycaemia, however there was a high degree of heterogeneity between the studies. When detemir was compared with NPH, reductions in severe (RR 0.74, 95% CI 0.58 to 0.96) and nocturnal (RR 0.92, 95% CI 0.85 to 0.98) hypoglycaemia were observed, though there was no reduction in overall hypoglycaemia.

In a further meta-analysis of 20 RCTs of greater than 12 weeks duration comparing basal insulin analogues with NPH insulin, the mean reduction in HbA1c associated with the use of analogues was 0.07% (0.77 mmol/mol) (95% CI 0.13 (1.42) to 0.01 (0.11)).¹⁹⁸ On combining the eight trials that compared insulin detemir with NPH insulin, there was significantly less weight gain associated with the use of insulin detemir than NPH insulin (by 0.26 kg/m², 95% CI 0.06 to 0.47). Equivalent data were not available for glargine. There was no reduction in overall hypoglycaemia associated with the use of basal analogues, though reductions in severe (OR 0.73, 95% CI 0.6 to 0.89) and nocturnal (OR 0.69, 95% CI 0.55 to 0.86) hypoglycaemia were observed.

One recent 24 month RCT compared insulin detemir (n = 331) with NPH insulin (n = 166) as the basal insulin component of a basal bolus regimen. The reduction in HbA1c in association with insulin detemir was 0.22% (2.40 mmol/mol) (95% CI 0.41 (4.48) to 0.03 (0.33)). Risk of major and nocturnal hypoglycaemia with detemir was 69% and 46% lower respectively in comparison with NPH (p < 0.001).¹⁹⁹

One study showed greater patient satisfaction, though no change in quality of life, with the use of insulin glargine when compared with NPH.²⁰⁰

Comparison of insulin detemir and insulin glargine

In a 52 week study comparing insulin detemir and insulin glargine as the basal component of a basal bolus regimen in 443 patients with type 1 diabetes, there was no difference or change in HbA1c or rates of hypoglycaemia between the groups. According to the study protocol, two thirds of the detemir group completed the study on twice daily detemir.²⁰¹

In a 26 week study comparing twice daily detemir with once daily glargine as part of a basal bolus regimen in 320 subjects with type 1 diabetes, there was no difference in improvement in HbA1c at the end of the study. There was no difference in overall confirmed hypoglycaemia, however, severe and nocturnal hypoglycaemia were 72% and 32% lower, respectively, with detemir. There was no significant difference in body weight.²⁰²

In summary, basal insulin analogues appear to offer no clinically significant improvement in glycaemic control, but may offer reductions in severe and nocturnal hypoglycaemia. Insulin detemir may be associated with less weight gain than NPH insulin, but in many individuals will require twice daily dosing. It is important to interpret these findings in the context of cost; while an economic analysis of the benefits of basal insulin analogues in type 2 diabetes was undertaken (see section 6.10.2), insufficient data were available in type 1 diabetes for a similar analysis, however both insulin glargine and insulin detemir cost more than NPH insulin.

B Basal insulin analogues are recommended in adults with type 1 diabetes who are experiencing severe or nocturnal hypoglycaemia and who are using an intensified insulin regimen. Adults with type 1 diabetes who are not experiencing severe or nocturnal hypoglycaemia may use basal analogues or NPH insulin.

1++

1++

1+

1++

1+

1+

Rapid-acting insulin analogues in children and adolescents

There are relatively few good quality studies in pre-pubertal children and adolescents comparing use of insulin analogues with that of regular human insulin. Even these few are of relatively short duration, and most involve small numbers of subjects.

One systematic review identified four studies in pre-pubertal children and one study involving adolescents which showed no difference in glycaemic control (as measured by HbA1c) between the use of rapid-acting insulin analogues and regular human insulin.¹⁹⁶ 1++

Overall and nocturnal rates of hypoglycaemia in pre-pubertal children and adolescents using rapid-acting insulin analogues were not significantly different from those using regular human insulin.¹⁹⁶ One study showed reduction in rates of both overall and nocturnal hypoglycaemia when using rapid-acting insulin analogues.¹⁹⁶ 1++

A meta-analysis which reviewed the same studies as the systematic review with one additional RCT included, also showed no significant difference between HbA1c or hypoglycaemia between rapid-acting analogues or regular human insulin.¹⁹⁵ 1++

Basal insulin analogues in children and adolescents

In both children and adolescents, compared with NHS insulins, neither of the basal insulin analogues, glargine nor detemir, was associated with a significant difference in HbA1c.¹⁹⁵ No difference in hypoglycaemia was seen with glargine when compared with NPH insulin. In the one trial comparing detemir with NPH in pre-pubertal children and adolescents, no differences in severe hypoglycaemia were observed though there were minor reductions in nocturnal and overall hypoglycaemia.²⁰³ 1++
1+

In children and adolescents, use of rapid-acting and basal insulin analogues offers at least similar glycaemic control, rates of overall hypoglycaemia, and rates of nocturnal hypoglycaemia to that of regular human insulin, and so both may be offered as alternatives.

The use of insulin in pregnant women with diabetes is discussed in section 7.5.2.

B Children and adolescents may use either insulin analogues (rapid-acting and basal), regular human insulin and NPH preparations or an appropriate combination of these.

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

CSII therapy

Continuous subcutaneous insulin infusion (CSII) or 'insulin pump' therapy allows programmed insulin delivery with multiple basal infusion rates and flexible bolus dosing of insulin with meals. In developed countries its usage is increasing in patients with type 1 diabetes, who are expert at carbohydrate counting or have undertaken an appropriate structured education course. CSII therapy requires considerable input especially from nurse specialists and dietitians in addition to the purchase of a pump and consumables.

A number of meta-analyses have evaluated trials of CSII therapy.²⁰⁴⁻²⁰⁹ The RCTs have often been of poor quality but performed in specialised pump centres. Concern has been raised over the lack of independently funded studies to allow objective comparison of results.²⁰⁹

One meta-analysis included six RCTs, all with patients <21 years of age,²⁰⁷ while the other meta-analyses included a mixture of infants, children, adolescents and adults and did not allow a comparison between the groups,^{204-206, 208} except for a significant increase in minor hypoglycaemia in children on CSII in one meta-analysis.²⁰⁹ 1++

In patients with type 1 diabetes CSII therapy has been associated with an improvement in glycaemic control with falls in HbA1c of between 0.2 to 0.4% (2.2 to 4.4 mmol/mol) compared to multiple daily injections (MDI), predominately using human insulin.²⁰⁶⁻²⁰⁹ 1+
1++

No differences in rates of diabetic ketoacidosis or severe hypoglycaemia were associated with CSII in comparison to MDI, with the exception of one meta-analysis which pre-selected studies to include people experiencing a high rate of hypoglycaemia on MDI.²⁰⁵ Severe hypoglycaemia was defined as that requiring third party assistance, including unconsciousness, seizure, glucagon administration and emergency attendance or admission to hospital. Trials were included where the rate of severe hypoglycaemia during MDI was > 10 episodes/100 patient years of treatment. The meta-analysis reported that CSII was associated with at least a threefold lower rate of severe hypoglycaemia (rate ratio 2.89). This study combined six RCTs with 'before and after' studies and noted an overall HbA1c reduction of 0.6% (6.6 mmol/mol) in favour of CSII.

1+

In one systematic review CSII therapy was shown to be of no benefit in quality of life (QoL).²¹⁰ Lack of benefit was ascribed to poor study quality, lack of power, lack of exclusion and inclusion criteria, mixture of patient groups and differing assessment of QoL tools. In particular the authors note the confounding role of structured education, which should be given to all people with diabetes before commencing CSII, but which may not be given to comparator groups if there are any. In 'before and after' studies, it is difficult to say how much of the benefit is due to the education rather than to the CSII.

1+

Three small RCTs have shown some benefit in treatment satisfaction associated with CSII despite no difference in glycaemic control.²¹¹⁻²¹³

In one crossover study, established users of CSII therapy were randomised to either continuing CSII or MDI. Despite no differences in HbA1c or episodes of severe hypoglycaemia, patients using CSII therapy had a greater mean treatment satisfaction score than those using MDI (mean \pm SD, 32.3 ± 2.6 v 23.2 ± 7.0 , $p < 0.0001$).²¹¹ Due to dropouts this study was underpowered to detect a significant difference in the primary outcome.

1+

One RCT randomised 72 newly diagnosed children and adolescents with type 1 diabetes to CSII or MDI.²¹² After 24 months no differences in HbA1c or rate of hypoglycaemia were reported between groups, but mean treatment satisfaction (\pm standard deviation (SD)) was significantly higher in the CSII group compared with the MDI group (33.1 ± 0.9 and 27.5 ± 2.0 , respectively, $p < 0.001$).

1+

A third small RCT also showed no difference in HbA1c or rates of hypoglycaemia between CSII and MDI groups.²¹³ The mean treatment satisfaction score (\pm SD) increased from 22.8 ± 8.1 at baseline to 31.5 ± 4.9 at 24 weeks in the CSII group and from 24.0 ± 6.3 to 28.8 ± 5.4 in the MDI group (treatment difference: 3.1, 95% CI 0.1 to 6.1, $p = 0.042$).

1+

Large RCTs comparing CSII therapy to MDI therapy with insulin analogues, which assess glycaemic control and rates of both hypoglycaemia and DKA are lacking. Such studies should not restrict entry on the basis of hypoglycaemia and should use a validated QoL assessment. One such study, the REPOSE (Relative Effectiveness of Pumps Over MDI and Structured Education) trial is likely to recruit patients in 2010.

A CSII therapy is associated with modest improvements in glycaemic control and should be considered for patients unable to achieve their glycaemic targets.

B CSII therapy should be considered in patients who experience recurring episodes of severe hypoglycaemia.

An insulin pump is recommended for those with very low basal insulin requirements (such as infants and very young children), for whom even small doses of basal insulin analogue may result in hypoglycaemia.

Pump therapy should be available from a local multidisciplinary pump clinic for patients who have undertaken structured education.

Targets for improvement in HbA1c and/or reduction in hypoglycaemia should be agreed by patients using CSII therapy and their multidisciplinary diabetes care team. Progress against targets should be monitored and, if appropriate, alternative treatment strategies should be offered.

5.3.3 DIETARY MANAGEMENT

A regimen which includes dietary management improves glycaemic control. Limited evidence was identified concerning the optimal type of dietary therapy.^{6,194} 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 type 1 diabetes.

Carbohydrate counting is an essential skill to support intensified insulin management in type 1 diabetes, either by MDI or CSII, and all patients must be able to access such training locally, and ideally, at their own diabetes clinic.

5.3.4 INPATIENT MANAGEMENT

One RCT of 300 people with type 1 and type 2 diabetes cared for by either hospital diabetes specialist nurses or general healthcare professionals, showed a length of stay (LoS) in hospital reduced by three days in those managed by the diabetes specialists (median LoS: intervention group 8 days, control group 11 days, $p < 0.01$).²¹⁴

1+

Inpatients with diabetes should have evaluation of their glycaemic control and support in the management of their diabetes from a diabetes nurse specialist in an effort to reduce length of stay.

No studies were identified looking at the impact of self or carer care compared to routine care on length of stay or patient satisfaction.

5.3.5 INTEGRATED CARE PATHWAYS IN DIABETIC KETOACIDOSIS

One cohort study of 43 people admitted with DKA reported an improvement in time to insulin and fluid administration but was underpowered to show change in length of stay, hypoglycaemia or morbidity.²¹⁵

2-

Children and young people with type 1 diabetes presenting with DKA should be managed according to local protocols which have been developed with reference to national and internationally agreed consensus documents.^{216, 217}

4

5.3.6 OUT OF HOURS SUPPORT

Experience of dedicated diabetes hotlines shows that parents of younger children and those with a shorter duration of diabetes are more likely to use this service.^{218, 219} There is no evidence suggesting that a dedicated diabetes helpline prevents acute complications and hospital admissions.

3

4

There are several different methods of providing advice and support to those diagnosed with type 1 diabetes in Scotland. These include the national NHS24 service, local GP or specialist nurse services, secondary care advice provided by on-call specialist nursing or medical staff or medical trainees after hours, and a commercial service provided by Novo Nordisk, staffed by independent specialist nurses.

People with diabetes should have access to medical advice 24 hours per day as part of their care package.

5.3.7 TRANSITION FROM PAEDIATRIC TO ADULT SERVICES

Young people with diabetes often move from the paediatric services to the adult healthcare system at a time when diabetes control is known to deteriorate.²²⁰ There is consensus that the needs of adolescents and young people need to be actively managed during this transition period.^{157, 221-224} Transition models have evolved according to local circumstances and beliefs and their complexity makes comparison very difficult. There is little evidence available on the different adolescent transition models and their benefits and there is no evidence to recommend a particular transition model.

3
4

Some common themes appear in the literature:

- Patients and their families favour a structured transition from paediatric to adult services together with adequate information along the way.
- A structured transition process appears to improve clinic attendance and reduces loss to follow up in the adult services.^{224,225}

- Paediatric and adult services should work together to develop structured transition arrangements that serve the needs of the local population.

5.3.8 MANAGEMENT OF DIABETES AT SCHOOL

Children spend 30-40% of their time within the education system, outside the direct supervision of their parents. Those adults responsible for them during school hours may not be experienced in the care of children with diabetes. Complications such as hypoglycaemia and poor glycaemic control may occur during these times.²²⁶

3

Only two studies were identified which addressed whether supportive management for children with type 1 diabetes within the education system has any effect on diabetes complications or glycaemic control. Both took place in the United States of America (USA), and therefore have limited generalisability to the United Kingdom (UK). The first study involved school-based consultations from the diabetes nurse, but was described as a pilot study, with no control group and a self-selected intervention group. The intervention consisted of increased visits during school hours to discuss diabetes and advice on dose adjustments. No changes in HbA1c or self-efficacy measurements were found.²²⁷ The second study involved increased school nurse supervision of children with poorly controlled diabetes. The intervention group showed a decrease in HbA1c of 1.6%, but an accompanying change of insulin regimen in this group (to MDI) may have biased the outcome.²²⁸

2-
1-

There is insufficient evidence to recommend specific supportive measures for children during school hours, but children should be afforded the same level of diabetes care whether in or out of school. Intensification of diabetes management requires increased monitoring and insulin use and, as this significantly improves glycaemic control, should be available to all children while at school.

- Educational and health services should work together to ensure that children with diabetes have the same quality of care within the school day as outside of it. Children at school should be supported with all necessary aspects of diabetes care, such as glucose monitoring, insulin injection and treatment of hypoglycaemia.

5.4 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.^{229,230} Frequency of insulin dose adjustment does not appear to affect quality of life.^{192,229-231}

1+

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

5.5 LONG TERM COMPLICATIONS AND SCREENING

5.5.1 RISK OF MICROVASCULAR COMPLICATIONS

Early abnormalities in children and adolescents (eg microalbuminuria, background retinopathy) predict later development of long term microvascular complications.^{6, 194, 232, 233}

2+

Maintaining glycaemic control to as near normal as possible significantly reduces the long term risk of microvascular diseases.^{6,194} Poor glycaemic control (HbA1c > 10% (86 mmol/mol)) over time in young people with diabetes increases the risk of the development of retinopathy by approximately eightfold.¹⁹⁴

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.

5.5.2 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.

Recommendations for screening patients with type 1 diabetes for retinopathy, nephropathy and hypertension are included in sections 10.2, 9.3 and 8.3 respectively.

There is no evidence that routine screening for autonomic neuropathy or hyperlipidaemia are of benefit in children and adolescents with type 1 diabetes.

5.5.3 CYSTIC FIBROSIS AND DIABETES

Twenty per cent of patients with cystic fibrosis will develop secondary diabetes by the age of 20, with an incidence which increases thereafter to 80% by the age of 35.²³⁴ Limited data suggest that clinical symptoms deteriorate when diabetes develops in cystic fibrosis,^{235,236} 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.

5.5.4 ASSOCIATED CONDITIONS

Thyroid and coeliac disease are reported to be increased in young people with type 1 diabetes compared with non-diabetic subjects.²³⁷⁻²³⁹ 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 diabetes and 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.

5.6 CHECKLIST FOR PROVISION OF INFORMATION

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

People with type 1 diabetes:

- should have the right to choose not just the insulin regimen, but whether to use an analogue (designer insulin), human or animal insulin. People with diabetes must appreciate the time action profiles of their type of insulin, have knowledge of injection sites and absorption rates of insulin.
- need to perform blood glucose monitoring at home on a regular basis and act on the results to adjust insulin therapy and achieve their target HbA1c levels.
- should initially receive intensive dietetic input with regular dietetic updates.
- should have a clear understanding of sick day rules and be able to recognise hypoglycaemia and treat it appropriately.

Ideally all of the above should form part of an education programme provided locally by the Diabetes Team, with the aim to empower patients to make the choice that is right for them.

People with type 1 diabetes:

- should have ongoing support for their diabetes.
- should have a clear plan of how to get help on an urgent or semi-urgent basis. This will often involve the local Diabetes Team in office hours, but outwith these times arrangements vary across Scotland.

Hospital admission- If you have concerns about your diabetes management as an inpatient ask the local ward staff to have the Diabetes Team review your progress.

Insulin and Driving- Patients starting insulin treatment must be advised to report this change to the DVLA (Driver and Vehicle Licensing Agency). Those taking insulin are required to reapply for their licence every 1-3 years with supportive evidence sought from their GP or consultant. Regular monitoring and prevention of hypoglycaemia are key to safe driving. Rules for driving should be discussed with healthcare professionals.

Healthcare professionals should:

- develop a local transition process that facilitates a seamless move to an adult service, which encourages regular attendance of teenagers.
- monitor emergency metabolic admissions.
- help promote good diabetes care in the school environment.
- provide a record of results obtained and targets issued for individual patients in a hand-held record.

6 Pharmacological management of glycaemic control in people with type 2 diabetes

This section of the guideline focuses on: (i) optimal targets for glucose control for the prevention of microvascular and macrovascular complications; and, (ii) the risks and benefits of the glucose-lowering agents (oral/injectable) and insulins currently available for those who require measures beyond diet and exercise to achieve targets. Review of individual therapeutic classes is an addition (rather than an update) to SIGN 55. An algorithm to guide choice of first, second and third line glucose-lowering agent which incorporates the summarised evidence and the clinical experience of the guideline development group is provided (see section 6.11).

6.1 INTRODUCTION

The immediate purpose of lowering blood glucose is to provide relief from symptoms (thirst, polyuria, nocturia, and blurred vision). Thereafter, the aim is to prevent microvascular complications: loss of vision (retinopathy), renal failure (nephropathy), and foot ulceration (neuropathy). High blood glucose (hyperglycaemia) is also one of the features of diabetes - with raised blood pressure and cholesterol - associated with macrovascular complications (myocardial infarction, stroke, and peripheral arterial disease). The effects of glucose-lowering therapies on cardiovascular morbidity and mortality are therefore of major importance and not necessarily related to glucose-lowering. Unfortunately, the majority of clinical trials to date have focused narrowly on glucose control (as assessed by HbA1c concentrations), and on the risks of weight gain and hypoglycaemia.

6.2 TARGETS FOR GLYCAEMIC CONTROL

Reducing HbA1c levels is associated with a reduction in microvascular and macrovascular complications in patients with type 2 diabetes. Several studies have assessed the benefit of intensive glycaemic control on cardiovascular risk and other outcomes, in particular by achievement of predefined HbA1c targets ranging from 6.4% (46 mmol/mol) to 8.0% (64 mmol/mol). Studies that were not primarily designed to compare intensive glycaemic control versus a less intensive strategy were not considered to contribute to the evidence base informing optimal glycaemic targets.

The United Kingdom Prospective Diabetes Study 33 (UKPDS 33) examined the effects of sulphonylureas, metformin and insulin over a median 10 year period in people with newly diagnosed diabetes. Mean HbA1c was lowered to 7.0% (53 mmol/mol) in the intensive arm compared to 7.9% (63 mmol/mol) in the conventional treatment group.²⁴⁰ In UKPDS 34, HbA1c was lowered to 7.4% (57 mmol/mol) in a subgroup of overweight people who were randomised to metformin compared with 8.0% (64 mmol/mol) in the conventional therapy group.²⁴¹

1+

The Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE) study used modified release gliclazide (MR) then increased metformin, thiazolidinedione, acarbose and insulin (initial basal with prandial added as required) to reduce HbA1c to a mean of 6.5% (48 mmol/mol) compared with a mean of 7.3% (56 mmol/mol) from a baseline of 7.5% (58 mmol/mol) by aiming for a target of < 6.5% (48 mmol/mol) as compared with standard care. Mean duration of diabetes in this trial was 7.9 years.²⁴²

1+

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study used the standard range of presently available therapy (including sulphonylureas, metformin, thiazolidinediones, insulin, DPP-4 inhibitors and exenatide) to reduce HbA1c rapidly to a mean of 6.4% (46 mmol/mol) compared with a mean of 7.5% (58 mmol/mol) from a baseline of 8.3% (67 mmol/mol) by aiming for a target of 6.0% (42 mmol/mol) as compared with a target of 7.0 to 7.9% (53 to 63 mmol/mol). Mean duration of diabetes in this trial was 10 years.²⁴³

1+

	<p>The Veterans Affairs Diabetes Trial (VADT) compared an intensive treatment strategy (maximal doses of metformin and rosiglitazone for people with BMI ≥ 27 kg/m²; maximal doses of glimepiride and rosiglitazone for people with BMI < 27 kg/m²; insulin added in if HbA1c $> 6\%$ (42 mmol/mol) with a standard treatment strategy (half maximal doses of same agents; insulin added in if HbA1c $> 9\%$ (74.9 mmol/mol)) in males with type 2 diabetes and baseline HbA1c 9.4% (79.2 mmol/mol). Achieved HbA1c levels were 6.9% (51.9 mmol/mol) and 8.4% (68.3 mmol/mol) respectively.²⁴⁴</p>	1+
6.2.1	MORTALITY	
	<p>Reducing blood glucose to specific mean HbA1c targets did not significantly reduce mortality during follow up in most RCTs; however, there was a 36% relative risk reduction (95% CI 9% to 55%) in all-cause mortality associated with intensive metformin treatment in UKPDS 34.²⁴¹ In the study (ACCORD) with the lowest mean HbA1c attained in the intensive treatment group (6.4% (46 mmol/mol)) treatment was stopped early as mortality in this group was significantly higher than in the usual care group (hazard ratios, HR 1.22, 95% CI 1.01 to 1.46 for all-cause mortality; and 1.35, 95% CI 1.04 to 1.76 for cardiovascular disease mortality).²⁴³ The excess mortality may have occurred as a consequence of rapid reduction of HbA1c rather than the absolute value attained but there is no evidence to show that more gradual reduction of HbA1c to the same target is associated with lower mortality.</p>	1+
	<p>Ten year post-randomisation follow up of UKPDS 33 and 34 suggested a long term beneficial effect of more intensive glycaemic control in the early years after diagnosis of diabetes despite similar control in intensive and conventional groups after study close-out.²⁴⁵ Reductions in all-cause mortality were reported for people treated with sulphonylurea or insulin (RR 13%, $p=0.007$) and for people treated with metformin (RR 27%, $p=0.002$).</p>	2+
6.2.2	CARDIOVASCULAR RISK	
	<p>Two meta-analyses of the heterogeneous trials mentioned above have used different approaches to compare the effect of improved glycaemic control (reflected by achieved HbA1c of 6.4 to 7.0% (46.4 to 53.0 mmol/mol) in the intervention groups, compared to 7.3 to 8.4% (56.2 to 68.3 mmol/mol) in the control groups). One meta-analysis, using summary data and including the UKPDS metformin substudy, reported that intensive glycaemic control reduced the risk for cardiovascular disease (RR 0.90, 95% CI 0.83 to 0.98) but did not reduce the risk for all-cause mortality (RR 0.98, 95% CI 0.84 to 1.15), cardiovascular mortality (RR 0.97, 95% CI 0.76 to 1.24) or stroke (RR 0.98, 95% CI 0.86 to 1.11).²⁴⁶ The other meta-analysis, using individual level data and excluding the UKPDS metformin substudy, reported that intensive glycaemic control reduced the risk for major cardiovascular disease (HR 0.91, 95% CI 0.84 to 0.99), mainly because of a 15% reduced risk of myocardial infarction (HR 0.85, 95% CI 0.76 to 0.94), but did not reduce the risk for all-cause mortality (HR 1.04, 95% CI 0.90 to 1.20), cardiovascular mortality (HR 1.10, 95% CI 0.84 to 1.42), stroke (HR 0.96, 95% CI 0.83 to 1.1) or hospitalised/fatal heart failure (HR 1.00, 95% CI 0.86 to 1.16).²⁴⁷</p>	1++
6.2.3	MICROVASCULAR MORBIDITY	
	<p>Several RCTs showed that reduction of HbA1c to a mean level of 6.4 to 8.0% (46 to 64 mmol/mol) reduces microvascular disease morbidity. The ADVANCE trial showed that the absolute risk of major microvascular outcomes (worsening or new retinopathy or nephropathy) decreased by 1.5% (RR reduction 14%, CI 3% to 23%).²⁴² The VADT reported reduction in microalbuminuria with absolute risk (AR) reduction of 2.5% ($p=0.05$).²⁴⁴ The UKPDS 33 showed a 25% relative risk reduction in aggregate microvascular endpoints (95% CI 7% to 40%).²⁴⁰</p>	1+
6.2.4	HYPOGLYCAEMIA	
	<p>Treatment to glycaemic targets increases incidence of hypoglycaemia. Significantly more episodes were reported in intensive versus conventional therapy groups in most studies, eg 10.5% v 3.5% for hypoglycaemia requiring medical assistance in the ACCORD trial ($p < 0.001$),²⁴³ 2.7% v 1.5% in the ADVANCE trial (HR 1.86, 95% CI 1.42 to 2.40).²⁴² UKPDS 33 showed a higher rate of major hypoglycaemia in patients on insulin or sulphonylureas than diet alone (insulin 1.8%, chlorpropamide 1.0%, glibenclamide 1.4%, diet 0.7%).²⁴⁰</p>	1+

6.2.5 WEIGHT GAIN

Patients who were allocated to intensive control groups gained more weight or were heavier at follow up than conventional treatment groups in most studies (see Table 1).

Table 1: Trials of intensive therapy to achieve glycaemic control

Trial (duration)	Weight gain (kg)	
	Intensive therapy group	Conventional therapy group
ACCORD ²⁴³ (3 years)	3.5	0.4
ADVANCE ²⁴² (median 5 years)	0.0	-1.0
UKPDS 33 ²⁴⁰ (median 10 years)	5.6	2.5
UKPDS 34 ²⁴¹ (median 10.7 years)	Not specified	
VADT ²⁴⁴ (median 5.6 years)	8.2	4.1

A An HbA1c target of 7.0% (53 mmol/mol) among people with type 2 diabetes is reasonable to reduce risk of microvascular disease and macrovascular disease. A target of 6.5% (48 mmol/mol) may be appropriate at diagnosis. Targets should be set for individuals in order to balance benefits with harms, in particular hypoglycaemia and weight gain.

6.3 METFORMIN

Metformin decreases hepatic glucose production and may improve peripheral glucose disposal while suppressing appetite and promoting weight reduction. Activation of the energy-regulating enzyme AMP-kinase in liver and muscle is a principal mode of action.

6.3.1 GLYCAEMIC CONTROL COMPARED TO PLACEBO (OR DIET)

One systematic review considered the effectiveness of metformin monotherapy compared with placebo or any active combination.²⁴⁸ When compared with placebo, metformin showed more benefit for HbA1c (standardised mean difference, SMD -0.97% (-10.60 mmol/mol), 95% CI -1.25 (-13.66) to -0.69 (-7.54)), and FPG (SMD -0.87, 95% CI -1.13 to -0.61), but there were no significant differences for BMI or weight, total cholesterol, high density lipoprotein (HDL) cholesterol, LDL cholesterol, triglycerides, or blood pressure.

1++

When compared with diet, metformin showed more benefit for HbA1c (SMD -1.06% (-11.58 mmol/mol), 95% CI -1.89 (-20.66) to -0.22 (-2.40)) and total cholesterol but no difference for FPG, BMI or weight, HDL cholesterol, LDL cholesterol, triglycerides, or blood pressure.

6.3.2 GLYCAEMIC CONTROL COMPARED WITH OTHER GLUCOSE-LOWERING AGENTS

The results of two large systematic reviews taken together suggest that metformin and sulphonylureas have similar effects on HbA1c.^{248, 249} In the first, participants using metformin showed marginally larger reductions in HbA1c compared with those using sulphonylureas (SMD -0.14% (-1.53 mmol/mol), 95% CI -0.28 (-3.06) to -0.01 (-0.11)).²⁴⁸ In the second, second-generation sulphonylureas were associated with a trend towards greater HbA1c reduction than with metformin (SMD -0.09%, 95% CI -0.30 to 0.10, not statistically significant).²⁴⁹ There was no significant difference in HbA1c between those using metformin and those using insulin, meglitinides or alpha-glucosidase inhibitors.²⁴⁸

1++

In non-obese patients metformin monotherapy reduced postprandial glycaemia in a similar way to repaglinide and was significantly more effective in reducing postprandial hypercholesterolaemia and hyperinsulinaemia.²⁵⁰

6.3.3 HYPOGLYCAEMIA/WEIGHT GAIN/ADVERSE EFFECTS

The main adverse event reported more frequently with metformin compared with placebo in one systematic review was diarrhoea (absolute risk increase ARI 6.8%; RR 3.09, 95% CI 1.58 to 6.07). Hypoglycaemia was reported more frequently with metformin compared with diet (ARI 2.9%; RR 4.21, 95% CI 1.40 to 12.66).²⁴⁸

1++

A systematic review of the risk of lactic acidosis with metformin found no cases of fatal or non-fatal lactic acidosis in 274 comparative trials and cohort studies amounting to 59,321 patient-years of metformin use. It estimated that the upper limit of the true incidence of lactic acidosis per 100,000 patient years was 5.1 compared with 5.8 in the non-metformin group. Furthermore, there was no difference in lactate levels for metformin compared with non-metformin therapies.²⁵¹

1++

There has been some controversy about the impact of tight glycaemic control in patients with type 2 diabetes and heart failure. A recent systematic review found two studies showing a significant improvement in outcome in patients allocated metformin compared with sulphonylureas and concluded that metformin was the only glucose-lowering agent not associated with harm in this group²⁵² (see section 8.5.1).

1++

6.3.4 CARDIOVASCULAR MORBIDITY

The UKPDS 34 allocated patients to either conventional (initial dietary modification with addition of a sulphonylurea for fasting plasma glucose > 15 mmol/l) or a more intensive glycaemic control strategy (which could include metformin, sulphonylurea or insulin therapy). For overweight patients (54% with obesity), those allocated to metformin (n=342) had improved outcomes compared with those on conventional treatment (n=411), for any diabetes-related outcomes (RR 0.68, 95% CI 0.58 to 0.87), diabetes-related death (RR 0.58, 95% CI 0.37 to 0.91) and all-cause mortality (RR 0.64, 95% CI 0.45 to 0.91).²⁴¹ The metformin group also had a significantly reduced risk of myocardial infarction (RR 0.61, 95% CI 0.41 to 0.89). There were no significant differences between metformin and other comparison arms for other outcomes such as stroke, peripheral arterial disease and microvascular disease.

1++

Despite the benefits of metformin for overweight patients in comparison with a conventional treatment strategy, no benefits were observed for any of the above outcomes for comparisons between intensive treatment with metformin and intensive treatment with chlorpropamide, glibenclamide, or insulin (n=951).²⁴¹

1++

Thus, while the data for clinically relevant outcomes with metformin are limited, they are stronger than for any other available oral agent for the treatment of type 2 diabetes. They underpinned the recommendation in SIGN 55 of metformin as 'first line' oral therapy in people with type 2 diabetes, which is retained in the present update.

A Metformin should be considered as the first line oral treatment option for overweight patients with type 2 diabetes.

6.4 SULPHONYLUREAS

Sulphonylureas increase endogenous release of insulin from pancreatic β -cells. The drugs available are classed according to their date of release: first generation (acetohexamide, chlorpropamide, tolbutamide, tolazamide) and second generation (glipizide, gliclazide, glibenclamide (glyburide), gliquidone, glycopyramide, glimepiride). First generation agents are now rarely used in the UK.

6.4.1 GLYCAEMIC CONTROL

UKPDS 33 showed that the sulphonylureas chlorpropamide and glibenclamide were more effective at reducing HbA1c than diet alone.²⁴⁰ Placebo comparator studies with newer sulphonylureas showed benefit in HbA1c but these were largely short duration trials of less than six months. One systematic review demonstrated a significant reduction in HbA1c with glibenclamide versus placebo.²⁵³

1+

The results of two large systematic reviews taken together suggest that metformin and sulphonylureas have similar effects on HbA1c.^{248, 249} In the first, participants using metformin showed marginally larger reductions in HbA1c compared with those using sulphonylureas (SMD -0.14% (-1.53 mmol/mol), 95% CI -0.28 (-3.06) to -0.01 (-0.11)).²⁴⁸ In the second, second-generation sulphonylureas were associated with a trend towards greater HbA1c reduction than with metformin (SMD -0.09%, 95% CI -0.30 to 0.10, not statistically significant).²⁴⁹

1++

Gliclazide MR and glimepiride were shown to be equally effective at reducing HbA1c at 27 weeks. HbA1c was not reduced further by glimepiride versus the longer established agent glibenclamide over 12-15 months.²⁵⁴

1+

A meta-analysis of six short term studies including 1,364 patients suggested that sulphonylureas can achieve significant improvements in glycaemic control when added to metformin in patients who have inadequate glycaemic control.²⁵⁵

1++

6.4.2 HYPOGLYCAEMIA/ WEIGHT GAIN/ADVERSE EFFECTS

UKPDS 33 showed a higher rate of major hypoglycaemia (defined as requiring third party help or medical intervention) in patients on sulphonylureas than diet alone (see section 6.2.4) and weight gain was greater (chlorpropamide 2.6 kg, glibenclamide 1.7 kg).²⁴⁰ A Scottish population based study showed that one person with type 2 diabetes in every 100 treated with a sulphonylurea each year experienced an episode of major hypoglycaemia, compared with one in every 2,000 treated with metformin and one in every 10 treated with insulin.²⁵⁶ One RCT over 27 weeks showed a significant reduction in confirmed hypoglycaemia (<3 mmol/l) with gliclazide MR versus glimepiride, while body weight increase was equivalent.²⁵⁴ One systematic review reported no confirmed episodes of hypoglycaemia (defined as plasma glucose \leq 3.3 mmol) with either glimepiride or placebo over 14 weeks. Reported hypoglycaemic symptoms and confirmed hypoglycaemia were no more frequent compared with placebo in patients taking glipizide and glimepiride over 3 to 4 months. Weight gain of 4.8 kg was observed in the glimepiride arm versus placebo.²⁵³

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3

6.4.3 CARDIOVASCULAR MORBIDITY

Concerns dating from the early 1970s regarding the cardiovascular safety of sulphonylureas continue to receive support from observational evidence. For example, in one large retrospective cohort study, there was a 24-61% excess risk for all-cause mortality with sulphonylureas in comparison with metformin.²⁵⁷

2+

In overweight participants of UKPDS 34 (see sections 6.2 and 6.3.4), non-statistically significant trends were observed for rates of diabetes-related death, all-cause mortality, myocardial infarction and stroke to be higher for an intensive treatment strategy based on sulphonylureas or insulin than for an intensive treatment strategy based on metformin.²⁴¹ However, in comparisons of intensive treatment strategies versus conventional treatment by agents used for the seven major UKPDS outcomes, the only mean relative risk higher than unity was for stroke when treatment was based on sulphonylureas or insulin (RR 1.14, 95% CI 0.70 to 1.84, not statistically significant).

1+

One RCT examining oral agents used as monotherapy in recently-diagnosed individuals (A Diabetes Outcome Progression, ADOPT trial) reported lower rates of cardiovascular disease adverse events over four years follow up with glibenclamide than with metformin or rosiglitazone (n = 41, 58, and 62 respectively; only the comparison between glibenclamide and rosiglitazone was statistically significant (p < 0.05)).²⁵⁸ Although 4,360 individuals were randomised, the study was not designed to examine cardiovascular disease and therefore had insufficient formal statistical power for this outcome.

1+

A Sulphonylureas should be considered as first line oral agents in patients who are not overweight, who are intolerant of, or have contraindications to, metformin.

6.5 THIAZOLIDINEDIONES

Thiazolidinediones increase whole-body insulin sensitivity by activating nuclear receptors and promoting esterification and storage of circulating free fatty acids in subcutaneous adipose tissue. Two thiazolidinediones are available for use in the UK - pioglitazone and rosiglitazone.

Pioglitazone

6.5.1 GLYCAEMIC CONTROL

Pioglitazone is effective at lowering HbA1c as monotherapy and in dual or triple therapy when combined with metformin, sulphonylurea or insulin.²⁵⁹ Combination therapy using doses of 15-30 mg daily have been shown to lower HbA1c by between 0.64 to 1.26% (6.99 to 13.77 mmol/mol).²⁶⁰

1++

6.5.2 CARDIOVASCULAR MORBIDITY

A Cochrane systematic review reported insufficient evidence to draw conclusions on the effect of pioglitazone on outcomes such as mortality, morbidity, adverse events or health-related quality of life.²⁶¹

1++

A subgroup analysis from the PROactive trial suggested a reduction in fatal and non-fatal MI in the subgroup with previous myocardial infarction (n = 2,445, HR 0.72, 95% CI 0.52 to 0.99, p = 0.045; NNT = 51 (95% CI 26 to 2,634)).²⁶² In patients with previous stroke (n = 984), subgroup analysis showed that pioglitazone reduced fatal or non-fatal stroke (HR 0.53, 95% CI 0.34 to 0.85, p = 0.0085; NNT = 21, 95% CI 12 to 75), while there was no effect on stroke risk in patients with no history of prior stroke (HR 1.06, 95% CI 0.73 to 1.52, p = 0.767).²⁶³

1+

However, a meta-analysis of 84 published and 10 unpublished trials of pioglitazone compared with placebo or other therapy, and excluding the PROactive trial, reported a reduction of all-cause mortality with pioglitazone (OR 0.30, 95% CI 0.14 to 0.63, p < 0.05), but no significant effect on non-fatal coronary events.²⁶⁴ A further meta-analysis with 16,390 patients found a reduction in the primary composite endpoint (death, MI or stroke) with pioglitazone compared with control (HR 0.82, 95% CI 0.72 to 0.94, p = 0.005).²⁶⁵

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A meta-analysis of studies on congestive heart failure (CHF) found an increased risk of CHF with all thiazolidinediones (TZDs) when compared with placebo or other medications, with an overall RR of 1.72 (95% CI 1.21 to 2.42).²⁶⁶ The relative risk was higher for rosiglitazone (2.18, 95% CI 1.44 to 3.32) than for pioglitazone (1.32, 95% CI 1.04 to 1.68).

1+

These findings are corroborated by further data from a manufacturer-sponsored meta-analysis including 16,390 patients.²⁶⁵ Serious heart failure was increased with pioglitazone (200 patients (2.3%) v 139 patients in control group (1.8%)) (HR 1.41, 95% CI 1.14 to 1.76, p = 0.002).

1-

The PROactive study found that, although more patients treated with pioglitazone had a serious heart failure event compared with placebo (p = 0.007), mortality due to heart failure was similar.²⁶⁷

1-

A study comparing pioglitazone to glibenclamide in patients with known grade II or III New York Heart Association (NYHA) functional class heart failure found more hospitalisations with pioglitazone (9.9%) than glibenclamide (4.7%) but no difference in mortality.²⁶⁸

1+

6.5.3 HYPOGLYCAEMIA/WEIGHT GAIN/ADVERSE EFFECTS

A systematic review of 18 RCTs with 11,565 participants providing loosely defined data on oedema reported a raised incidence of oedema (RR 2.86, 95% CI 2.14 to 3.18).²⁶¹ This finding has been supported by other meta-analyses.^{260, 266, 269, 270}

1++

Pioglitazone is associated with weight gain.²⁶⁰

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One meta-analysis of five RCTs of duration one to four years reported fractures in 5.8% of women with type 2 diabetes treated with TZDs in comparison with 3.0% treated with other agents (OR 2.23, 95% CI 1.65 to 3.01). In this meta-analysis there was no increase in rates of fracture in men (OR 1.00, 95% CI 0.73 to 1.39).²⁷¹

1++

One prospective population based cohort study confirmed TZD use compared with sulphonylurea use was associated with a 28% increased risk of peripheral fracture in both men and women (HR 1.28, 95% CI 1.10 to 1.48).²⁷² 2+

A Pioglitazone can be added to metformin and sulphonylurea therapy, or substituted for either in cases of intolerance.

A Pioglitazone should not be used in patients with heart failure.

B The risk of fracture should be considered in the long term care of female patients treated with pioglitazone.

Patients prescribed pioglitazone should be made aware of the increased risk of peripheral oedema.

Rosiglitazone

6.5.4 GLYCAEMIC CONTROL

Rosiglitazone is effective at lowering HbA1c when used as combination therapy with metformin and/or sulphonylureas (SU),^{249,260} and when used as monotherapy.²⁶⁹ Combination therapy using doses of 4 mg and 8 mg of rosiglitazone daily have been shown to lower HbA1c by between 0.75 to 1.08% (8.20 to 11.80 mmol/mol).²⁶⁰ There is no convincing evidence that rosiglitazone monotherapy has benefits over metformin or SU monotherapy.²⁷³ 1++

6.5.5 CARDIOVASCULAR MORBIDITY

Several meta-analyses raised a concern that rosiglitazone therapy, compared with control, may increase the risk of severe cardiovascular disease or cardiovascular death in patients with type 2 diabetes. A Cochrane systematic review reported insufficient evidence to draw conclusions on the effect of rosiglitazone on outcomes such as mortality, morbidity, adverse events or health-related quality of life.²⁷³ 1++

One meta-analysis reported a non-significant increase in cardiovascular death (OR 1.64, 95% CI 0.98 to 2.74) but a borderline significant increase in MI (OR 1.43, 95% CI 1.03 to 1.98) in patients taking rosiglitazone, compared with those on metformin or a sulphonylurea, or placebo.²⁷⁴ Further meta-analyses found similar non-significant elevations in odds ratios, eg a mean OR of cardiovascular death varying from 1.17 to 1.64 (dependent on statistical technique) (95% CI 0.77 to 2.74) and a mean OR of 1.26 to 1.43 (dependent on statistical technique) (95% CI 0.93 to 1.98) for myocardial infarction.^{275,276} It should be noted that while these mean estimates show consistent trends, they are not elevated statistically. 1+ 1++

In the largest RCT examining cardiovascular outcomes with rosiglitazone therapy (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes, RECORD), 4,447 people with type 2 diabetes were randomised to rosiglitazone-based therapy versus combination therapy with metformin and sulphonylureas. In this prospective open-label non-inferiority trial 321 of those randomised to rosiglitazone experienced cardiovascular hospitalisation or death versus 323 in the control group (HR 0.99, 95% CI 0.85 to 1.16). The study was powered to exclude a 20% or greater excess risk of cardiovascular disease with rosiglitazone (as predefined by the investigators). The overall event rate was substantially lower than anticipated in the study protocol power calculation, meaning the trial had less statistical power than initially planned. Nonetheless, the CI for the primary endpoint hazard ratio excluded the predefined 20% excess risk; therefore it is not known whether rosiglitazone could be associated with an excess risk smaller than 20%. The hazard ratio for myocardial infarction was elevated non-significantly at 1.14 (95% CI 0.80 to 1.63), the hazard ratio for CHF was 2.10 (95% CI 1.35 to 3.27) while the hazard ratio for stroke was 0.72 (95% CI 0.49 to 1.06). Findings from the pre-specified subgroup analyses of the primary endpoint suggested a possible but not statistically significant increase of cardiovascular events with rosiglitazone in patients with previous ischaemic heart disease (HR 1.26, 95% CI 0.95 to 1.68, $p=0.055$).²⁷⁷ 1-

Patients taking rosiglitazone have a greater risk of congestive heart failure when compared with placebo, metformin or sulphonylureas. Meta-analyses have reported an increased absolute risk of CHF of 0.7 to 2.2% in patients taking rosiglitazone and increased hazard ratios in observational studies comparing patients taking any thiazolidinedione compared with patients taking any other glucose-lowering agent (HR 1.06 to 2.27).^{249, 269} A further meta-analysis showed patients taking either thiazolidinedione had an increased risk of CHF compared with controls (RR 1.72, 95% CI 1.21 to 2.42, p=0.002) but no increased risk of cardiovascular death.²⁶⁶

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6.5.6 HYPOGLYCAEMIA/WEIGHT GAIN/ADVERSE EFFECTS

Rosiglitazone treatment is associated with weight gain^{249, 273} and oedema.^{249, 260,270,273}

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One meta-analysis reported TZD use to be associated with an increased risk of peripheral fracture among women with type 2 diabetes (OR 2.23, 95% CI 1.65 to 3.01). In this meta-analysis there was no increased risk in men (OR 1.00, 95% CI 0.73 to 1.39).²⁷¹

1++

One prospective population based cohort study confirmed TZD use compared to sulphonylurea use was associated with a 28% increased risk of peripheral fracture in both men and women (HR 1.28, 95% CI 1.10 to 1.48).²⁷²

2+

Analysis of ADOPT revealed that rosiglitazone use versus comparator was associated with an increased risk of peripheral fractures in women (HR versus metformin 1.81, 95% CI 1.17 to 2.80; HR versus glyburide 2.13, 95% CI 1.30 to 3.51).²⁵⁸ Similar analysis of RECORD confirmed the ADOPT findings (RR versus control 1.57, 95% CI 1.26 to 1.97; RR for women 1.82, 95% CI 1.37 to 2.41; RR for men 1.23, 95% 0.85 to 1.77).²⁷⁷

1-

In September 2010 the European Medicines Agency (EMA) completed a review of rosiglitazone-containing medicines at the request of the European Commission, following reports of an increase in the risk of cardiovascular problems with rosiglitazone. The Agency’s Committee for Medicinal Products for Human Use (CHMP) concluded that, at present, the benefits of rosiglitazone do not outweigh its risks, and that the marketing authorization for all rosiglitazone-containing medicines should be suspended across the European Union (EU). Further information about the suspension can be found at the EMA web site (<http://bit.ly/Rosi2011>).

In February 2011 the U.S. Food and Drug Administration (FDA) notified the public that information on the cardiovascular risks of rosiglitazone has been added to the physician labeling and patient Medication Guide. From Spring 2011, the FDA is expected to announce that rosiglitazone and rosiglitazone-containing medicines should only be used:

- In patients already being treated with these medicines
- In patients whose blood sugar cannot be controlled with other anti-diabetic medicines and who, after consulting with their healthcare professional, do not wish to use pioglitazone-containing medicines.

6.6 DIPEPTIDYL PEPTIDASE-4 INHIBITORS

Dipeptidyl peptidase-4 inhibitors are oral agents which inhibit activity of the enzyme DPP-4 and hence prolong the actions of endogenous Glucagon Like Peptide 1 (GLP-1) (see section 6.9). There are three DPP-4 inhibitors currently available: sitagliptin, vildagliptin and saxagliptin.

6.6.1 GLYCAEMIC CONTROL

Compared with placebo, sitagliptin, vildagliptin and saxagliptin were shown to be effective at lowering HbA1c by 0.7% (7.65 mmol/mol), 0.6% (6.56 mmol/mol) and 0.6% (6.56 mmol/mol) respectively.²⁷⁸⁻²⁸⁰ These data include studies where DPP-4 inhibitors have been used as monotherapy v placebo,²⁷⁸⁻²⁸⁰ dual therapy in combination with metformin, sulphonylurea or thiazolidinedione v placebo²⁷⁸⁻²⁸⁰ and for sitagliptin as triple therapy in combination with metformin and sulphonylurea.²⁸¹

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The glucose-lowering effect of sitagliptin (100 mg/day) added to metformin (1.5 g/day) in a 52 week study was equivalent (non-inferior) to combination therapy with glipizide 10 mg/day and metformin 1.5 g/day.²⁸² The glucose-lowering effects of vildagliptin compared with other oral agents have demonstrated similar (non-inferior) glucose-lowering over 6-24 months in the following treatment comparisons: vildagliptin 100 mg/day versus either metformin 2 g/day^{278, 283} pioglitazone 30 mg/day²⁷⁸ or rosiglitazone 8 mg/day.²⁸⁴ Similar glucose-lowering was also demonstrated when vildagliptin 100 mg/day or other agents (pioglitazone 30 mg/day²⁸⁵ or glimepiride 6 mg/day) were used in combination with metformin ≥ 1.5 /day.²⁸⁶

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6.6.2 HYPOGLYCAEMIA/ WEIGHT GAIN/ADVERSE EFFECTS

Systematic reviews of DPP-4 inhibitor trials have shown that both DPP-4 inhibitors were well tolerated with no difference in discontinuation rates due to adverse events between sitagliptin or vildagliptin intervention and control groups.^{278, 287} No severe hypoglycaemia was reported in study participants taking DPP-4 inhibitors. In combination with metformin, rates of hypoglycaemia were six to tenfold lower with sitagliptin²⁸² or vildagliptin²⁸⁶ than with sulphonylureas.

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A Cochrane review reported a statistically significant increase in all-cause infection following treatment with sitagliptin (RR 1.29, 95% CI 1.09 to 1.52, $p = 0.003$) but not following treatment with vildagliptin (RR 1.04, 95% CI 0.87 to 1.24, $p = 0.7$).²⁷⁸ Regulatory authorities have advised continued post-marketing surveillance.

1++

In studies of at least 24 weeks duration, sitagliptin and vildagliptin were shown to be weight neutral.^{278, 287}

1++

6.6.3 CARDIOVASCULAR MORBIDITY AND MORTALITY

Published studies for sitagliptin and vildagliptin have medium term follow up (maximum of two years) therefore the long term effects of these drugs on microvascular complications, cardiovascular disease and mortality are unknown.

A DPP-4 inhibitors may be used to improve blood glucose control in people with type 2 diabetes.

6.7 ALPHA-GLUCOSIDASE INHIBITORS

Alpha-glucosidase inhibitors are oral glucose-lowering agents that specifically inhibit alpha-glucosidases in the brush border of the small intestine. These enzymes are essential for the release of glucose from more complex carbohydrates.

The evidence for alpha-glucosidase inhibitors was obtained from three high quality systematic reviews^{249, 269, 288} and one further RCT.²⁸⁹ The majority of data reviewed examined alpha-glucosidase inhibitors as monotherapy in the management of patients with type 2 diabetes. Few studies were long term in determining the impact of a therapy for a chronic condition. The largest evidence base for the use of alpha-glucosidase inhibitors is with acarbose. There are no peer-reviewed data available on the long term effects of alpha-glucosidase inhibitors in terms of mortality, morbidity and quality of life.

6.7.1 GLYCAEMIC CONTROL

Acarbose monotherapy reduces HbA1c when compared with placebo.^{249, 269, 288} One meta-analysis reported lowering by 0.8% (8.7 mmol/mol) (95% CI 0.9 (9.8) to 0.6% (6.6), 28 comparisons) compared with placebo.²⁸⁸

1++

Alpha-glucosidase inhibitors inhibit postprandial glucose peaks thereby leading to decreased post load insulin levels especially when compared with sulphonylureas.²⁸⁸ However, a small number of head-to-head trials and indirect data have shown that alpha-glucosidase inhibitors may be less efficacious in reducing hemoglobin HbA1c than other monotherapy regimens (acarbose versus sulphonylurea, absolute reduction 0.75% (8.20 mmol/mol), 95% CI 1.02 (11.15) to 0.48 (5.25)).²⁴⁹

1++

Trials comparing acarbose and sulphonylureas tend to have been performed using sulphonylureas at sub-therapeutic doses limiting the strength of the conclusions. There is not enough robust evidence with studies using therapeutic doses to determine categorically which treatment is the more effective. There are insufficient large randomised controlled trials of long duration that compare alpha-glucosidase inhibitors with other glucose-lowering agents.

6.7.2 HYPOGLYCAEMIA/ WEIGHT GAIN/ADVERSE EFFECTS

Compared with placebo, alpha-glucosidase inhibitors have minimal effects on body weight.^{249, 269, 288} Abdominal discomfort (flatulence, diarrhoea and stomach ache) are the most frequently occurring adverse effects of alpha-glucosidase inhibitors and are dose related (acarbose ARI 25.8%, OR 3.3, 95% CI 2.3 to 4.7). As predicted from their mechanism of action, hypoglycaemic adverse effects do not occur.²⁸⁸ The prevalence of gastrointestinal symptoms associated with acarbose (range, 15% to 30%) is similar to that with metformin and higher than that with thiazolidinediones or sulphonylureas (< 3 trials for each comparison).²⁶⁹ One RCT reported an incidence of 51% of patients reporting adverse events.²⁸⁹

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B Alpha-glucosidase inhibitors can be used as monotherapy for the treatment of patients with type 2 diabetes if tolerated.

6.8 MEGLITINIDES

Meglitinides act on the same β -cell receptor as sulphonylureas but have a different chemical structure.

6.8.1 GLYCAEMIC CONTROL

In a systematic review of studies comparing meglitinides to placebo, both repaglinide and nateglinide resulted in improved glycaemic control but produced a higher incidence of minor hypoglycaemic events.²⁹⁰ Metformin used in combination with different doses of nateglinide produced significantly lower glycaemic values than metformin monotherapy. Two studies compared repaglinide with nateglinide and found that the former was more effective in improving glycaemic control after 16 weeks. No studies reported the effect of meglitinides on mortality or diabetes-related complications.

1++

The systematic review included three trials that compared repaglinide with metformin and reported similar improvements in glycaemic control.

One study compared nateglinide with gliclazide as add-on therapy to metformin in patients inadequately controlled on the latter. There were no significant differences in glycaemic control.²⁹¹

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Meglitinides have not been assessed for their long term effectiveness in decreasing microvascular or macrovascular risk and are more expensive than other glucose-lowering agents.²⁹²

6.8.2 HYPOGLYCAEMIA/WEIGHT GAIN/ADVERSE EFFECTS

No differences in body weight were reported in studies comparing meglitinides with placebo. Weight gain was more common (up to 3 kg in three months) and hypoglycaemia was more frequent in those treated with meglitinides compared with metformin.²⁹⁰

1++

6.9 GLUCAGON LIKE PEPTIDE-1 AGONISTS

Glucagon Like Peptide (GLP)-1 is one of the key 'incretin' hormones - a group of rapidly metabolised peptides secreted from the gut in response to food which amplify secretion of insulin from pancreatic β -cells and inhibit inappropriate glucagon secretion. They also slow gastric emptying, resulting in slower absorption of glucose following meals, and reduce appetite. GLP-1 agonists mimic endogenous GLP-1 activity but are resistant to breakdown by the DPP-4 enzyme, resulting in more prolonged action.

6.9.1 GLYCAEMIC CONTROL

Two GLP-1 agonists are currently available: exenatide, which requires twice daily injection and has a half-life of four hours, and liraglutide, which requires once daily injection and has a half-life of 11-13 hours.

Three placebo-controlled RCTs of 26 weeks duration were reported in a meta-analysis which demonstrated that in people with type 2 diabetes (disease duration 6-9 years, baseline BMI 30-34 kg/m²) exenatide (10 mcg twice daily) compared with placebo added to oral glucose-lowering agents (metformin and/or sulphonylurea) significantly reduced HbA1c (WMD for change in HbA1c from baseline -0.95% (-10.38 mmol/mol), 95% CI -1.21 (-13.22) to -0.7 (-7.65)).²⁸⁷ Those with a baseline HbA1c > 9% (75 mmol/mol) had a larger reduction in HbA1c.

1++

Four placebo-controlled RCTs of 26 weeks duration reported in a meta-analysis demonstrated that in people with type 2 diabetes (disease duration 5-9 years, baseline BMI 30.0-33.5 kg m²) liraglutide (1.2-1.8 mg once daily) compared with placebo added to oral glucose-lowering agents (metformin and/or sulphonyurea or metformin and thiazolidinediones) significantly reduced HbA1c (WMD for change in HbA1c from baseline -1.0% (-10.93 mmol/mol), 95% CI -1.1 (-12.02) to -0.8 (-8.74)).²⁹³

1++

A meta-analysis reported data from two studies comparing exenatide therapy with insulin therapy. In both trials exenatide therapy added to oral glucose-lowering agents was compared with once or twice daily insulin added to oral glucose-lowering agents. Both exenatide and insulin therapy added to oral glucose-lowering agents resulted in a similar reduction in HbA1c, (WMD for change in HbA1c from baseline -0.06% (-0.66 mmol/mol), 95% CI -0.22 (-2.4) to 0.1 (1.09)).²⁸⁷

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A meta-analysis of two RCTs of 26 and 52 weeks duration, respectively, comparing liraglutide (1.2-1.8 mg once daily) with glimepiride (4-8 mg daily) reported no significant difference in HbA1c at study endpoint.²⁹³

1++

In one RCT of 26 weeks duration, liraglutide 1.8 mg once daily added to oral glucose-lowering agents (metformin and sulphonylurea) reduced mean HbA1c by 1.12% (12.24 mmol/mol); in comparison exenatide 10 mcg twice daily reduced HbA1c by 0.79% (8.63 mmol/mol). The estimated treatment difference was -0.33% (-3.61 mmol/mol), (95% CI -0.47 (-5.14) to -0.18 (-1.97), $p < 0.0001$).²⁹⁴

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6.9.2 HYPOGLYCAEMIA/WEIGHT GAIN/ADVERSE EFFECTS

In the studies discussed above, GLP-1 agonists were generally well tolerated; the most frequent adverse events were gastrointestinal, especially nausea, which was generally reported as mild to moderate (OR 3.88 95% CI 2.79 to 5.42, $p < 0.001$).²⁹³ Severe hypoglycaemia was rare in exenatide and liraglutide studies and occurred only when sulphonylureas were co-prescribed.²⁹³ Mild to moderate hypoglycaemia was seen in 16% versus 7% of patients treated with exenatide versus placebo (risk ratio 2.3; 95% CI 1.1 to 4.9).²⁸⁷ In one study, 25.5% of patients treated with liraglutide versus 33.6% of patients treated with exenatide reported minor hypoglycaemia, $p = 0.01$.²⁹⁴

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There is insufficient evidence to determine whether GLP-1 agonists increase background rates of acute pancreatitis.^{287, 293, 295}

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GLP-1 agonist treatment may result in weight loss. Weight loss is reported in study participants treated with exenatide over 24 to 52 weeks in the range of -1.6 to -3.1 kg.²⁹⁵⁻²⁹⁹ People with type 2 diabetes treated with exenatide 10 mcg twice daily versus liraglutide 1.8 mg once daily lost similar amounts of weight -2.87 kg (SE, 0.33) versus -3.24 kg (SE 0.33), estimated treatment difference -0.38 kg, 95% CI -0.99 to 0.23, $p = 0.2235$.²⁹⁴

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Hence, weight loss is a possible advantage of GLP-1 agonist therapy compared to insulin therapy and some oral glucose-lowering drugs, eg sulphonylureas and thiazolidinediones.

A **GLP-1 agonists (exenatide or liraglutide) may be used to improve glycaemic control in obese adults (BMI ≥ 30kg/m²) with type 2 diabetes who are already prescribed metformin and/or sulphonylureas. A GLP-1 agonist will usually be added as a third line agent in those who do not reach target glycaemia on dual therapy with metformin and sulphonylurea (as an alternative to adding insulin therapy).**

A **Liraglutide may be used as a third line agent to further improve glycaemic control in obese adults (BMI ≥ 30kg/m²) with type 2 diabetes who are already prescribed metformin and a thiazolidinedione and who do not reach target glycaemia.**

Careful clinical judgement must be applied in relation to people with long duration of type 2 diabetes on established oral glucose-lowering drugs with poor glycaemic control (> 10 years, these individuals being poorly represented in published studies) to ensure insulin therapy is not delayed inappropriately for the perceived benefits of GLP-1 agonists.

6.10 INSULIN

6.10.1 CONTINUING ORAL AGENTS WHEN INITIATING BASAL INSULIN

A systematic review showed that when starting insulin therapy, continuing metformin therapy is associated with lower HbA1c (by up to 0.6% (6.6 mmol/mol)) and less weight gain (by up to 3.7 kg) without an increase in the risk of hypoglycaemia.³⁰⁰ Continuing sulphonylurea therapy when starting once daily insulin monotherapy is associated with a greater HbA1c reduction (0.3% (3.3 mmol/mol), 95% CI 0.0 (0.0) to 0.6 (6.6)) than insulin monotherapy alone. Continuing metformin, or sulphonylurea or both, in combination resulted in lower insulin requirements by 46% (range -5% to 74%) compared with insulin monotherapy alone.

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A **Oral metformin and sulphonylurea therapy should be continued when insulin therapy is initiated to maintain or improve glycaemic control.**

6.10.2 INITIATING BASAL INSULIN: LONG-ACTING INSULIN ANALOGUES VERSUS INTERMEDIATE-ACTING HUMAN INSULIN

When starting insulin therapy as a single injection before bed-time, NPH insulin is as effective in reducing HbA1c as basal insulin analogue therapy.^{195, 301-304} However, basal insulin analogue therapy is associated with fewer episodes of nocturnal and overall hypoglycaemia (see table 2).³⁰⁴ No difference was seen for severe hypoglycaemia. Collating evidence from six short term trials, it was necessary to treat eight patients with type 2 diabetes (95% CI 6 to 11) with glargine compared with NPH (continuing oral agents) to avoid one episode of nocturnal hypoglycaemia.³⁰⁵ Weight gain was slightly less with detemir than with NPH insulin when added to oral glucose-lowering agents (1 kg, 95% CI -1.69 to -0.23 kg).¹⁹⁷

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In a UK health technology assessment of newer drugs for blood glucose control in type 2 diabetes, the incremental cost per quality adjusted life year (QALY) gained for use of glargine in place of NPH insulin was estimated at £320,029; for detemir the equivalent cost estimate was £417,625.³⁰⁴

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Table 2: Relative and absolute risk of nocturnal and overall hypoglycaemia associated with long-acting analogue and NPH insulins.

	Nocturnal hypoglycaemia		Overall hypoglycaemia	
	Glargine v NPH	Detemir v NPH	Glargine v NPH	Detemir v NPH
No of studies	7	4	7	4
No of patients on analogues	1,372	872	1,192	872
Total no of hypos in patients using analogues	247	176	550	392
No of patients on NPH	1,306	712	1,105	712
Total no of hypos in patients using NPH	418	282	603	434
Absolute risk reduction	14%	20%	9%	16%
Relative risk reduction	46% (95% CI 31 to 57%)	46% (95% CI 32 to 58%)	11% (95% CI 4 to 17%)	32% (95% CI 4 to 46%)

A Once daily bedtime NPH insulin should be used when adding insulin to metformin and/or sulphonylurea therapy. Basal insulin analogues should be considered if there are concerns regarding hypoglycaemia risk.

6.10.3 INSULIN INITIATION AND INTENSIFICATION: BASAL VERSUS PRANDIAL VERSUS PRE-MIXED INSULINS

In the largest (n=708) and longest (three year) randomised trial of complex insulin regimens to date ("4T"), three insulin initiation regimens (basal, prandial, and biphasic) were compared. The regimen was intensified (see below) after one year if necessary to achieve a target HbA1c of 6.5% (48 mmol/mol) (if HbA1c was unacceptably high this occurred earlier).³⁰⁶ Metformin and sulphonylureas were continued in all patients until the insulin intensification step, when sulphonylureas were stopped.

The basal insulin group commenced bedtime insulin detemir (or twice daily dosing if required) with bolus mealtime insulin aspart added at intensification. The prandial group started with mealtime insulin aspart three times a day with subsequent intensification by addition of insulin detemir. The biphasic insulin group initially received twice daily biphasic insulin aspart, with later intensification by addition of insulin aspart at lunchtime.

At three years, the basal initiation regimen (moving to additional prandial insulin) resulted in the best combination of outcomes. HbA1c reduction was equivalent to either basal or prandial (6.9% (52 mmol/mol), 95% CI 6.6 (49) to 7.1 (54) v 6.8% (51 mmol/mol), 95% CI 6.6 (49) to 7.0 (53)); however, with the basal regimen there were fewer episodes per patient per year of grade 2 and 3 hypoglycaemia (median 1.7, 95% CI 1.3 to 2.0 v 5.7, 95% CI 4.3 to 7.0) with less weight gain (basal 3.6 kg v 6.4 kg, p<0.001). In comparison with biphasic insulin, the basal regimen resulted in lower HbA1c (7.1% (54 mmol/mol), 95% CI 6.9 (52) to 7.3 (56)), less weight gain (5.7 kg, p=0.005) and less hypoglycaemia (3 episodes (2.3 to 4.0) per patient per year) despite higher insulin doses (1.21, 95% CI 1.08 to 1.34 v 0.86, 95% CI 0.71 to 1.01 u/kg/day).

A When commencing insulin therapy, bedtime basal insulin should be initiated and the dose titrated against morning (fasting) glucose. If the HbA1c level does not reach target then addition of prandial insulin should be considered.

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6.10.4 INTENSIFYING INSULIN THERAPY: PRE-MIXED PREPARATIONS

Adding in rapid-acting insulin in a pre-mixed biphasic preparation results in lower HbA1c than with basal analogue therapy alone (HbA1c difference -0.39% (-4.26 mmol/mol), 95% CI -0.5 (-5.50) to -0.28 (-3.06)).^{307, 308} However, the dose titration algorithms used in nine of the 11 trials in one meta-analysis resulted in higher insulin doses being administered in those receiving pre-mixed biphasic insulin preparations compared with basal insulin analogue therapy.³⁰⁷ Consequently, there was a greater risk of hypoglycaemia (OR 2.02, 95% CI 1.35 to 3.04) and significantly greater weight gain (mean 0.6 to 1.9 kg in three studies with pre-mixed insulin analogues compared with basal insulin analogues).³⁰⁹

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- Aim to optimise insulin dose and regimen to achieve target glycaemia while minimising the risk of hypoglycaemia and weight gain.

6.10.5 INTENSIFYING INSULIN THERAPY: RAPID-ACTING INSULIN ANALOGUES VERSUS HUMAN INSULIN

No difference in HbA1c reduction has been demonstrated between pre-mixed preparations containing rapid-acting analogues compared with those containing regular insulin (HbA1c difference -0.05% (-0.55 mmol/mol), 95% CI -0.15 (-1.64) to 0.04 (0.44)), although there was a borderline increase in rates of hypoglycaemia (OR 1.5, 95% CI 1.0 to 2.26) with analogue mixtures.³⁰⁷ In four times daily (“basal-bolus”) regimens, regular insulin is as effective as rapid-acting analogue insulin for HbA1c reduction, with no difference in rates of hypoglycaemia.^{195, 196, 310}

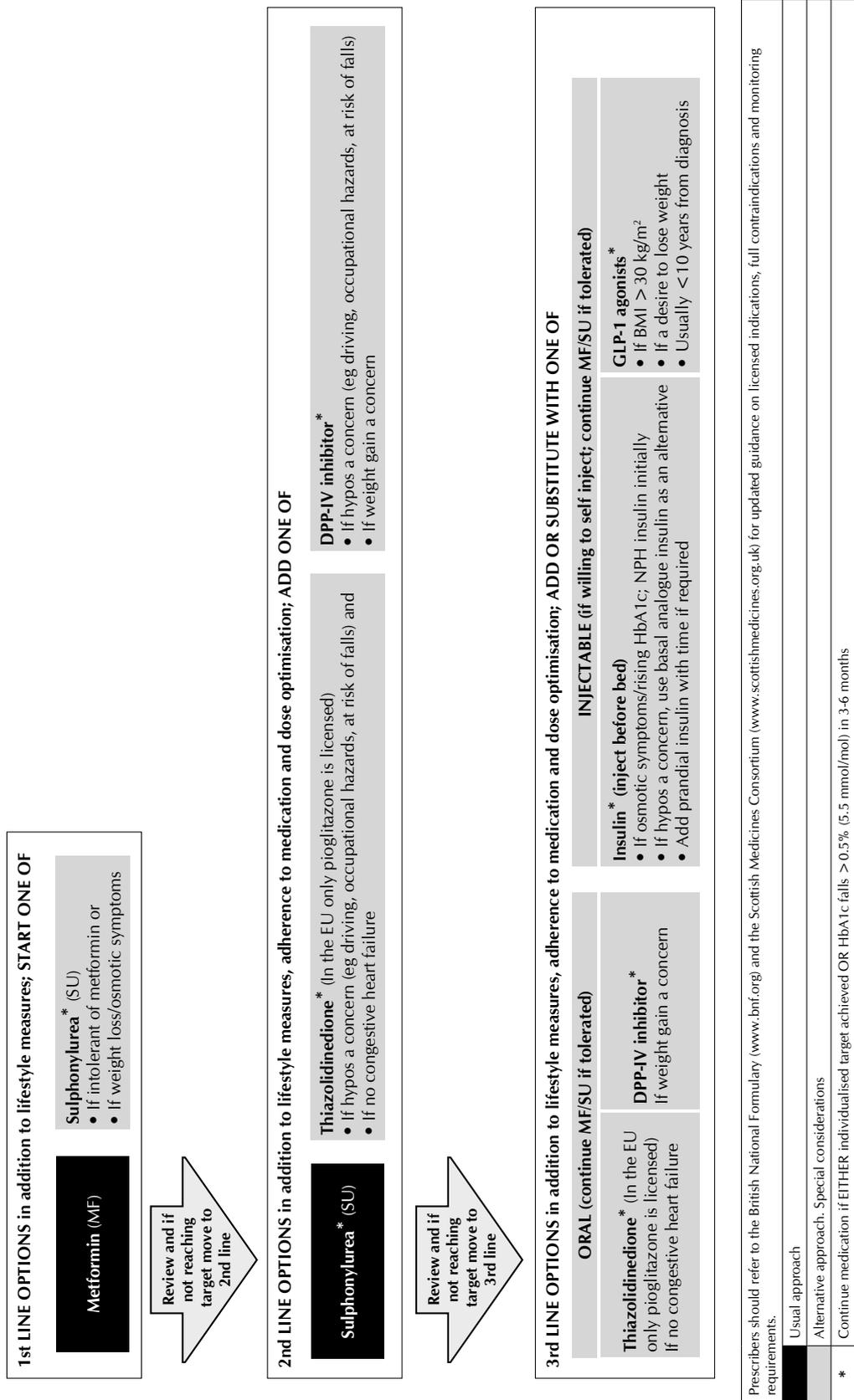
1⁺

- A** Soluble human insulin or rapid-acting insulin analogues can be used when intensifying insulin regimens to improve or maintain glycaemic control.

- When intensifying insulin therapy by addition of rapid-acting insulin, sulphonylurea therapy should be stopped.

6.11 ALGORITHM FOR GLUCOSE-LOWERING IN PEOPLE WITH TYPE 2 DIABETES

REVIEW AND SET GLYCAEMIC TARGET: HbA1c <7% (53 mmol/mol) OR INDIVIDUALISED AS AGREED



6.12 CHECKLIST FOR PROVISION OF INFORMATION

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

People with diabetes may have to take a range of oral and injectable medications each of which is associated with different properties and warnings. Information is presented below on each of the major classes of glucose-lowering agents. A number of oral agents are available in combination with each other in fixed dose combination. Using these preparations to decrease 'tablet burden' is convenient, and moreover is associated with increased concordance with therapy.

Principles

Therapeutic relationships established between people with diabetes and their healthcare professionals, together with agreement of individualised targets for care, are critical for realising the potential benefits of clinic consultations and resulting prescriptions. Wherever possible, members of the diabetes care team should adopt an open attitude of unconditional positive regard. In order that appropriate guidelines may be followed, people with diabetes should be advised to inform any healthcare professional from whom they are receiving treatment of their condition.

Metformin

Metformin should be taken with or immediately after a meal. It should be introduced in low dose, with gradual escalation (eg 500 mg once daily for one week, 500 mg twice daily in week two, 500 mg thrice daily in week three, and 1 g twice daily in week four). Some individuals may not tolerate higher doses, in which case dose reduction is appropriate. Nausea, diarrhoea, and abdominal pain are the most common adverse effects. People should be informed that these side effects often improve after a few days of continued therapy, or with a small dose reduction.

A modified release preparation (metformin MR) is also available suitable for once daily dosing; some individuals otherwise intolerant of metformin may find this more acceptable, or may in some cases be able to take higher doses.

Metformin should usually be discontinued during a severe illness (eg myocardial infarction, pneumonia, severe infection and/or dehydration) as it may aggravate tissue hypoxia and accumulate when renal function is impaired. In these circumstances, it may be appropriate to use other glucose-lowering therapies, including insulin, in which case admission to hospital may be required.

As iodine-containing contrast media may cause acute deterioration of renal function, local arrangements should be in place for discontinuation of metformin prior to radiological investigations using >100 ml of contrast or where serum creatinine is raised (see www.rcr.ac.uk/docs/radiology/pdf/IVcontrastPrintFinal.pdf).

Sulphonylureas

These agents (eg gliclazide, glimepride, glibenclamide) should ideally be taken 30 minutes before food. The main risk is hypoglycaemia. This risk is increased in older age groups, and in those with renal impairment and/or liver disease. Glibenclamide is particularly prone to causing hypoglycaemia and should not be used in the elderly. The warning signs of hypoglycaemia, which should be outlined to people taking these agents, include (early signs) tremor, sweating, shaking, irritability, and (later signs) lack of concentration or confusion.

Gliclazide is available in a modified release (MR) preparation. This permits once daily dosing even when higher doses are required. Prescribers should be aware that gliclazide MR 30 mg is therapeutically equivalent to standard gliclazide 80 mg (maximum dose therefore 120 mg once daily rather than 160 mg twice daily).

People taking sulphonylureas should also be advised of their propensity to cause weight gain and therefore the need, if possible, to avoid calorie excess.

Thiazolidinediones

People prescribed these agents (rosiglitazone, pioglitazone – ‘TZDs’) should be advised that they may cause ankle oedema in some individuals. Where this occurs, discontinuation is usually appropriate. People taking TZDs should also be advised of the likelihood of weight gain and increased risk of fracture, although these are not necessarily reasons for discontinuation.

DPP-4 inhibitors

These newer agents are generally well tolerated. However, questions remain about the possibility that they may predispose either to more frequent (usually minor) infections, or even acute pancreatitis. People prescribed these agents should therefore be encouraged to report potentially serious symptoms, particularly severe abdominal pain, and, where in doubt, to discontinue DPP-4 inhibitors pending prompt further assessment.

GLP-1 agonists

These newer agents require to be injected subcutaneously, like insulin. In keeping with the appetite-suppressant effect of these agents (exenatide, liraglutide) the most common adverse effects are nausea, vomiting and diarrhoea. Increased contact with the diabetes team is required particularly in the first weeks of use, usually with monitoring of therapeutic response – weight and HbA1c.

Hypoglycaemia is much less frequent than with insulin, but may occur with GLP-1 agonists, particularly when administered in combination with a sulphonylurea. When a GLP-1 agonist is added to a sulphonylurea, a reduction in sulphonylurea dose should be considered.

As there is a small risk of acute pancreatitis with these agents, people receiving these agents should be encouraged to report any unexpected or severe symptoms in order that therapy can be discontinued and appropriate investigation/treatment can be initiated promptly.

As for oral agents, people taking exenatide or liraglutide may hold a regular (Group 1) driving licence without restriction.

Acarbose

When acarbose is prescribed, people with diabetes should be advised of the likelihood of gastrointestinal symptoms, particularly abdominal pain, diarrhoea and wind. These symptoms mainly arise from the fermentation of undigested carbohydrates by colonic bacteria.

Insulin

See *section 5.6*

7 Management of diabetes in pregnancy

7.1 INTRODUCTION

An optimal outcome may be obtained from pregnancy in women with diabetes if excellent glycaemic control is achieved before and during pregnancy. However, type 1 and 2 diabetes are high risk states for both the woman and her fetus. There are increased complications of diabetes, severe hypoglycaemia, and progression of microvascular complications. Ketoacidosis must also be avoided. There are also increased risks of obstetric complications, such as miscarriage, maternal infection, pre-eclampsia, premature labour, polyhydramnios and failure to progress in first or second stage. Fetal and neonatal complications include congenital malformation, late intrauterine death, fetal distress, hypoglycaemia, respiratory distress syndrome and jaundice. Rates of fetal and neonatal loss and major congenital malformation are increased by at least two to threefold. The prevalence of type 2 diabetes is increasing in women of reproductive age and outcomes may be equivalent or worse than in those with type 1 diabetes. Management prior to and during pregnancy should follow the same intensive programme of metabolic, obstetric and neonatal supervision.

National audits on management of diabetes in pregnancy indicate that adverse pregnancy outcomes remain higher in women with diabetes than in the non-diabetic population.^{311, 312}

- An experienced multidisciplinary team, led by a named obstetrician and physician with an interest in diabetes, and including a diabetes specialist nurse, diabetes specialist midwife and dietitian should provide comprehensive care from pre-pregnancy to postnatal review.

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

7.2 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 these women. In general, the contraceptive advice for a woman with diabetes should follow that in the general population. The combined oral contraceptive (COC) is contraindicated in women with diabetes according to the presence and severity of diabetic complications and/or other risk factors for vascular disease. Progestogen-only preparations, oral or intramuscular, may be suitable in these women. The World Health Organization's evidence based guidance for medical eligibility criteria for contraceptive use makes recommendations for women with diabetes.³¹³

Long-acting methods such as implants, intrauterine systems (IUS) and copper intrauterine devices (IUD) are safe methods of contraception which may be particularly suitable for use in women with diabetes as these are as effective as sterilisation and produce low circulating hormone levels.³¹⁴

- Pregnancy should be planned and good contraceptive advice and pre-pregnancy counselling are essential.
- Healthcare professionals should refer to the WHO medical eligibility criteria for contraceptive use prior to offering contraceptive advice to women with diabetes.

4

7.3 PRE-PREGNANCY CARE

Infants whose mothers with diabetes received dedicated multidisciplinary pre-pregnancy care showed significantly fewer major congenital malformations (approximating to the rate in non-diabetic women) compared to infants whose mothers did not receive such care. Attendance at a pre-pregnancy clinic is associated with a reduction in the rate of miscarriage 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.^{315, 316}

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The essential components of a pre-pregnancy care programme include review and consideration of the medical (including pharmacological treatment), obstetric and gynaecological history; advice on glycaemic control to optimise HbA1c; screening for complications of diabetes and counselling for maternal and fetal complications.

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

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

No evidence was identified on structured education specifically for pre-pregnant women. Women contemplating pregnancy should have access to structured education in line with the commendations for adults with diabetes (see sections 3.2.1 and 3.2.3).

7.3.1 PRE-PREGNANCY TARGETS FOR BLOOD SUGAR

A large body of observational evidence found an association between maternal glycaemia and congenital malformation and miscarriage.³¹⁷ The risk of congenital anomaly in the offspring of women with pre-pregnancy diabetes increased with an increasing level of HbA1c.³¹⁸ In women with type 1 diabetes, poor glucose control before and during pregnancy is associated with perinatal mortality and congenital malformations (see Table 3).³¹⁹ No HbA1c threshold for such effects was identified.

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Table 3: Derived absolute risk of a major or minor congenital anomaly in association with the number of standard deviations (SD) of glycosylated haemoglobin above normal, and the approximate corresponding HbA1c concentration, measured periconceptionally.³¹⁸

SD of GHb	Corresponding HbA1c (%)	Corresponding HbA1c (mmol/mol)	Absolute risk of a congenital anomaly (% , 95% CI)
0	5.0	31	2.2 (0.0 to 4.4)
2	6.0	42	3.2 (0.4 to 6.1)
4	7.0	53	4.8 (1.0 to 8.6)
6	8.0	64	7.0 (1.7 to 12.3)
8	9.0	75	10.1 (2.3 to 17.8)
10	10.0	86	14.4 (2.8 to 25.9)
≥ 12	≥ 11	≥ 97	20.1 (3.0 to 37.1)

Assumes a DCCT-aligned HbA1c assay with mean (SD) of 5.0% (0.5%) among non-diabetic, non-pregnant controls. Copyright 2007 American Diabetes Association. From *Diabetes Care*, Vol. 30, 2007; 1920-1925. Reprinted with permission from *The American Diabetes Association*.³¹⁸

C Pre-pregnancy glycaemic control should be maintained as close to the non-diabetic range as possible, taking into account risk of maternal hypoglycaemia.

- The target for pre-pregnancy glycaemic control for most women should, as a minimum, be an HbA1c of less than 7% (53 mmol/mol) although lower targets of HbA1c may be appropriate if maternal hypoglycaemia can still be minimised.

7.3.2 ORAL MEDICATION BEFORE AND DURING PREGNANCY

Folic acid

Neural tube defects in high-risk pregnancies are associated with lower levels of folate.³²⁰ A large study in high-risk non-diabetic women has shown that prescription of 4 mg folate supplementation pre- and periconceptually has been shown to confer protection against neural tube defects, particularly in women at high risk.³²¹

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B All women with diabetes should be prescribed high dose pre-pregnancy folate supplementation, 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.

Metformin and sulphonylureas

Metformin and sulphonylureas are not associated with an increase in congenital malformation or early pregnancy loss.^{317, 322} Systematic reviews of observational studies on the use of oral hypoglycaemics (including metformin and glibenclamide) in women with diabetes in early pregnancy do not indicate an increase in miscarriage or congenital anomaly.^{323, 324}

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B Women with diabetes initially treated in early pregnancy with metformin or sulphonylureas should be advised that these medications do not appear to carry additional risk of teratogenesis or early pregnancy loss.

While metformin and glibenclamide may be used to treat GDM (gestational diabetes mellitus see section 7.8.3), sulphonylureas other than glibenclamide should not be used during pregnancy due to placental passage.

Statins

A reference guide to medications in pregnancy and lactation reported that atorvastatin, fluvastatin, pravastatin and simvastatin are contraindicated in pregnancy and lactation.³²⁵ The reference guide found that a small number of case reports and surveillance studies and a case series had investigated the use of atorvastatin, fluvastatin, pravastatin and simvastatin in pregnant women. The case series evaluated 20 cases of malformation in 54 cases of statin exposure reported to the US Food and Drug Administration between 1987 and 2001. The malformations included five major defects of the central nervous system (including two cases of holoprosencephaly) and five unilateral limb deficiencies.

4

No evidence was identified for rosuvastatin.

The British National Formulary recommends that statins should be avoided during pregnancy as congenital malformations have been reported and decreased synthesis of cholesterol may affect fetal development.⁵

ACE inhibitors

Angiotensin converting enzyme (ACE) inhibitors have been associated with an increase in risk of congenital malformation and both ACE inhibitors and angiotensin receptor blocking medications should be avoided throughout pregnancy.³²⁶

The use of statins, ACE inhibitors and angiotensin receptor blocking medications should be reviewed in women pre-pregnancy and avoided during pregnancy.

7.4 NUTRITIONAL MANAGEMENT

It is good clinical practice to provide dietary advice to women before, during and after pregnancy.³²⁷

4

Advice on diet and exercise should be offered in line with recommendations for adults with diabetes (see sections 3.7.1 and 3.5.4)

D Dietetic advice should be available in all diabetic antenatal clinics.

7.5 OPTIMISATION OF GLYCAEMIC CONTROL

7.5.1 GLUCOSE MONITORING

Optimal glucose control before pregnancy reduces congenital malformations and miscarriage, while during pregnancy it reduces macrosomia, stillbirth, neonatal hypoglycaemia, and respiratory distress syndrome.³²⁶

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D All women with pre-gestational diabetes should be encouraged to achieve excellent glycaemic control.

There is limited evidence comparing the use of preprandial testing to postprandial testing during pregnancy. A small RCT of 61 pregnant women with type 1 diabetes found that postprandial blood glucose monitoring was associated with greater success in achieving glycemic control targets and a smaller neonatal triceps skinfold thickness. A statistically significant reduction in the incidence of pre-eclampsia was associated with postprandial monitoring.³²⁸

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In women with gestational diabetes, measurement and targeting of postprandial glucose was associated with improved outcomes (including birth weight and macrosomia).³²⁹ Detection and management of gestational diabetes, including protocols specifying postprandial targets, were associated with reduced birth weight and reduced perinatal morbidity in two large randomised studies.^{330, 331}

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C Postprandial glucose monitoring should be carried out in pregnant women with gestational diabetes and may be considered in pregnant women with type 1 or 2 diabetes.

- In people with type 1 or type 2 diabetes, as long as hypoglycaemia can be minimised, aim to achieve blood glucose:
- between 4 and 6 mmol/l preprandially, and
 - <8 mmol/l one hour postprandially, or
 - <7 mmol/l two hours postprandially
 - >6 mmol/l before bed.

There is limited evidence that continuous glucose monitoring may be of benefit to women during pregnancy. Use of continuous glucose monitoring compared to conventional monitoring was associated with an improvement in birth weight and macrosomia in one study of women with type 1 and type 2 diabetes but not in another randomised control trial in women with gestational diabetes.^{332, 333}

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B Continuous glucose monitoring may be considered in women with type 1 and type 2 diabetes.

Diabetes specialist nurses and midwives have an important role in educating women on the need for home blood glucose monitoring 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.

7.5.2 INSULIN THERAPY

Intensive insulin therapy is beneficial in terms of maternal and neonatal outcomes.³³⁴ Use of insulin analogues outwith pregnancy is associated with limited evidence of reduction in hypoglycaemia (see sections 5 and 6).

It has been demonstrated that rapid-acting analogue insulins to confer potential advantages during pregnancy. Lispro and aspart have been associated with an improved glycaemic profile in the short term compared to unmodified short acting human insulin.³³⁵⁻³³⁷ A non-significant trend towards reduced major hypoglycaemic (RR 0.72) and nocturnal hypoglycaemic (RR 0.48) events was found with insulin aspart.^{338, 339} There appear to be no consistent safety concerns with respect to maternal or neonatal outcomes with rapid-acting insulin analogues.^{335, 336}

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No evidence was identified on the benefit of glulisine during pregnancy.

There is a lack of high quality evidence regarding outcomes of pregnancy using basal insulin analogue therapy or CSII in women who are pregnant. Current evidence suggests neither benefit nor harm with CSII.^{340, 341}

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No randomised control trial evidence is available to support the use of either of the basal insulin analogues detemir or glargine in women who are pregnant or considering pregnancy. Several case control studies suggest no increase in adverse outcomes with glargine.³⁴²⁻³⁴⁵

The choice of insulin therapy should be discussed, ideally as part of pre-pregnancy counselling.

B **Rapid-acting insulin analogues (*lispro and aspart*) appear safe in pregnancy and may be considered in individual patients where hypoglycaemia is problematic.**

NPH insulin should remain the basal insulin of choice in pregnancy unless the clinical benefit of a basal insulin analogue has been demonstrated on an individual basis.

Women should be advised that while most commonly used regular human insulins are licensed for use during pregnancy, other insulins and oral glucose-lowering agents (eg metformin, glibenclamide, other sulphonylureas, detemir) are not.

7.6 COMPLICATIONS DURING PREGNANCY

7.6.1 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.

7.6.2 METABOLIC COMPLICATIONS

During pregnancy, hypoglycaemic unawareness and severe hypoglycaemia are common. Diabetic ketoacidosis can develop more rapidly, at lower levels of blood glucose and in response to therapeutic glucocorticoids. Women and their partners need education on the management of hypoglycaemia, including the use of glucagon, avoiding hypoglycaemia during driving and on the recognition and prevention of ketoacidosis, which may result in fetal death. Local emergency contact arrangements must be explicit.

7.6.3 MICROVASCULAR COMPLICATIONS

Diabetic retinal and renal disease can deteriorate during pregnancy.³⁴⁶ The presence of retinopathy alone is not associated with a poorer pregnancy outcome for the fetus unless concurrent nephropathy is evident.³⁴⁷

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3**Retinopathy**

Prevention of visual impairment in people with type 1 and type 2 diabetes is covered in section 10.

In one study, 43% of women with baseline retinopathy showed progression during pregnancy,³⁴⁶ although sight-threatening retinopathy is rare (around 2% of pregnancies).³⁴⁸ Poor glycaemic control in the first trimester and pregnancy-induced or chronic hypertension are independently associated with the progression of retinopathy.³⁴⁶

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C Examination of the retina prior to conception and during each trimester is advised in women with type 1 and type 2 diabetes. More frequent assessment may be required in those with poor glycaemic control, hypertension or pre-existing retinopathy.

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

Multidisciplinary teams should have locally agreed protocols for the grade of retinopathy required for referral.

Parous women with type 1 diabetes have significantly lower levels of all retinopathy compared with nulliparous women.³⁴⁹ The associated significant difference in HbA1c 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.

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 a pre-pregnancy level within three months of delivery. The incidence of worsening chronic hypertension or pregnancy-induced hypertension/pre-eclampsia is high in women with both incipient and overt nephropathy, occurring in over 50% of women where overt nephropathy is present. Worsening nephropathy and superimposed pre-eclampsia are the most common causes of pre-term delivery in women with diabetes.³³¹

- Women with diabetic nephropathy require careful monitoring and management of blood pressure.
 - ACE inhibitors and angiotensin receptor blocking medications 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.

7.7 FETAL ASSESSMENT

An early pregnancy scan is considered good practice to confirm viability in women with pre-existing diabetes, particularly when changes in medication are required or diabetic control is suboptimal.

There is evidence of an increased incidence of congenital malformations in women with pre-existing diabetes (type 1 and type 2).³¹⁷⁻³¹⁹ In general, the sensitivity of ultrasound scanning for detecting structural abnormalities increases with gestational age.³⁵⁰ It is not possible to determine when during the second trimester scanning should take place to maximise detection rates. A detailed anomaly scan, including evaluation of the four chamber heart and outflow tracts, undertaken at around 20 weeks (18-22 weeks) enables detection of many major structural abnormalities.³⁵⁰

2⁺⁺

All women should be offered scanning to include:

- an early viability scan
- a gestational age scan between 11 weeks and 13 weeks (+6 days) in association with biochemical screening and nuchal translucency measurement to risk assess for trisomies.

B ▪ **a detailed anomaly scan including four chamber cardiac view and outflow tracts between 20 and 22 weeks.**

In pregnancies complicated by maternal diabetes, the fetus is at risk of both macrosomia and intrauterine growth restriction (IUGR). The risk of macrosomia is greater when there has been poor glycaemic control. The risk of IUGR is greater in women with vascular complications of diabetes (retinopathy, nephropathy) or when pre-eclampsia develops.³⁵¹

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Fetal monitoring includes cardiotocography (CTG), Doppler ultrasound and ultrasound measurement of fetal growth and liquor volume. Although regular fetal monitoring is common practice, no evidence has been identified on the effectiveness of any single or multiple techniques and therefore the clinical judgement of an obstetrician experienced in diabetic pregnancy is essential.

When IUGR is suspected, additional monitoring with serial ultrasound and umbilical arterial Doppler velocimetry is associated with improved outcomes (fewer inductions of labour and hospital admissions with a trend to improved perinatal mortality).³⁵²

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The evidence for the accuracy of ultrasound scanning in predicting macrosomia (birth weight >4,000 g) is mixed. The accuracy of fetal weight estimation in women with diabetes is at least comparable to women who are not diabetic,³⁵³ but for prediction of macrosomia sensitivities have been found to vary from 36-76%, and positive predictive values from 51-85%.³⁵³⁻³⁵⁸ The negative predictive value of ultrasound is consistently higher (80-96%) and therefore it is feasible that the true value of ultrasonography in the management of these women may be its ability to rule out the diagnosis of macrosomia.³⁵⁴⁻³⁵⁷

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There is evidence to suggest that the incorrect diagnosis of a large for gestational age fetus increases the induction and Caesarean section rate without improving clinical outcome.^{355, 356, 359} Studies conclude that the reliability of ultrasound estimation of fetal weight is suboptimal.^{357, 358, 360-362}

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The ability to predict shoulder dystocia in the non-diabetic population is poor and evidence in the diabetic population limited.³⁶³ Determination of polyhydramnios may be clinically useful as it may be associated with adverse clinical outcome.

In the management of gestational diabetes, four randomised control trials used ultrasound to detect abdominal circumference (AC) >70th or >75th percentile and/or abnormal glucose monitoring to select women for insulin initiation or intensification.³⁶⁴⁻³⁶⁷ The trials used differing levels of less intensive glycaemic management (where AC <70th or 75th percentile or glucose monitoring was within target) and more intensive glycaemic management (where AC >70th or 75th percentile or glucose monitoring was outwith target). The trials reported either equivalent outcomes or improved outcomes (birthweight, macrosomia, large for gestational age) in women with gestational diabetes.³⁶⁵⁻³⁶⁷ Improved outcomes were associated with AC being ascertained early (rather than late) in the third trimester and intensively managed thereafter.^{365, 367-369} Where outcomes were equivalent this was achieved with fewer women requiring insulin or a change of treatment assignment.^{366, 367} Although the rates of large for gestational age infants were reduced with insulin therapy there were no immediate clinical benefits observed from this reduction and an increase in the Caesarean section rate in the groups receiving intensive treatment was observed.^{364, 366}

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C Where IUGR is suspected, regular monitoring including growth scans and umbilical artery Doppler should be carried out.

In the absence of IUGR, monitoring of fetal growth can be used but given the inaccuracies in estimating fetal weight it is important that this is not used as a sole method of determining timing or mode of delivery.

7.8 GESTATIONAL DIABETES

Gestational diabetes 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.³⁷⁰ If type 1 or type 2 diabetes is presumed (eg due to early presentation or grossly elevated blood glucose), urgent action is required to normalise metabolism.

Two randomised control trials have shown that intervention in women with gestational diabetes with dietary advice, monitoring and management of blood glucose is effective in reducing birth weight and the rate of large for gestational age infants,^{330, 331} as well as perinatal morbidity.³³⁰ In a single study dietary therapy was associated with a reduction in the rate of large for gestational age infants, even with degrees of mild glucose intolerance short of current diagnostic criteria for gestational diabetes, although other outcomes (birth weight, macrosomia, neonatal hypoglycaemia) were not significantly affected.³⁷¹

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In older (non-randomised) series a diagnostic label of GDM was associated with an increased likelihood of induction of labour, instrumental delivery and Caesarean section.³⁷² The more recent RCTs of detection and management of GDM found no change in the rate of Caesarean section in one study,³³⁰ and a reduction in another.³³¹

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A A suitable programme to detect and treat gestational diabetes should be offered to all women in pregnancy.

The most appropriate strategies for screening and diagnosing GDM remain controversial. There is a continuous relationship between maternal glucose level (fasting, 1 hour and 2 hours after 75 g OGTT) at 24-28 weeks and pregnancy outcomes (macrosomia, fetal insulin, clinical neonatal hypoglycaemia and Caesarean section).³⁷³ Studies showing a benefit of screening to detect GDM have used a variety of strategies.^{330, 331}

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7.8.1 SCREENING FOR GDM

Early pregnancy

An important aim of screening, particularly in early pregnancy, is to identify women with undiagnosed type 2 diabetes. Clinical suspicion that type 1 or type 2 diabetes is present or developing in pregnancy may be raised by persistent heavy glycosuria in pregnancy (2+ on more than two occasions), random glucose >5.5 mmol/l two hours or more after food, or >7 mmol/l within two hours of food.³

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The International Association of Diabetes and Pregnancy Study Groups consensus document suggests that all or high-risk women should be offered screening with HbA1c, fasting or random glucose at the first gestational visit.³⁷⁴ While the characteristics of HbA1c in early pregnancy should be close to those outwith pregnancy, it should be noted that normal HbA1c falls in later pregnancy, potentially resulting in false negative results. While levels of glucose tolerance diagnostic of diabetes (HbA1c ≥6.5% (48 mmol/mol), fasting ≥7.0 mmol/l or two hours ≥11.1 mmol/l) can be interpreted in early pregnancy, the clinical interpretation of intermediate levels of glucose testing (HbA1c 6.0 to 6.4% (42 to 46 mmol/mol), fasting glucose 5.1 to 6.9 mmol/l, 2 hour glucose 7.8 to 11.0 mmol/l) encompassing current definitions of gestational diabetes, impaired fasting glucose and impaired glucose tolerance remain to be defined.

4

Later pregnancy

Controversy remains over the best screening strategy for detection of GDM and the most clinically and cost-effective strategy is likely to vary depending on the population. A number of risk factors can be identified and health economic analysis supports screening of women with risk factors using 75 g oral glucose tolerance test (OGTT) at 24-28 weeks of gestation (see Table 4).³²⁶ Measurement of fasting glucose provided a good predictor of adverse outcomes in the HAPO study.³⁷³

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It is expected that strategies to detect previously existing but undetected diabetes in early pregnancy and strategies to screen for gestational diabetes at 24-28 weeks will be refined as information on the characteristics of this testing becomes apparent for the local population. Strategies are likely to be simplified for women believed to be low risk based on risk factors (see Table 4).

Table 4: Risk factors for gestational diabetes³²⁶

BMI more than 30 kg/m ²
Previous macrosomic baby weighing 4.5 kg or more
Previous gestational diabetes
Family history of diabetes (first degree relative with diabetes)
Family origin with a high prevalence of diabetes: <ul style="list-style-type: none"> ▪ South Asian (specifically women whose country of family origin is India, Pakistan or Bangladesh) ▪ Black Caribbean ▪ Middle Eastern (specifically women whose country of family origin is Saudi Arabia, United Arab Emirates, Iraq, Jordan, Syria, Oman, Qatar, Kuwait, Lebanon or Egypt).

Screening at first antenatal visit

- ☑ At booking all women should be assessed for the presence of risk factors for gestational diabetes.
- ☑ All women with risk factors should have HbA1c or fasting glucose measured.
 - Women in early pregnancy with levels of HbA1c $\geq 6.5\%$ (48 mmol/mol), fasting ≥ 7.0 mmol/l or two hour ≥ 11.1 mmol/l glucose diagnostic of diabetes should be treated as having pre-existing diabetes.
 - Women with intermediate levels of glucose (HbA1c 6.0 to 6.4% or 42 to 46 mmol/mol), fasting glucose 5.1 to 6.9 mmol/l or two hour glucose 8.6 to 11.0 mmol/l should be assessed to determine the need for immediate home glucose monitoring and, if the diagnosis remains unclear, assessed for gestational diabetes by 75 g OGTT at 24-28 weeks.

Screening later in pregnancy

- ☑
 - All women with risk factors should have a 75 g OGTT at 24-28 weeks.
 - A fasting plasma glucose at 24-28 weeks is recommended in low-risk women.

7.8.2 DIAGNOSIS OF GDM

There is a continuous relationship between maternal glucose level (fasting, one hour, two hours after 75 g OGTT) and fetal growth.³⁷³

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It is likely that the greatest health benefits come from treating women with the highest levels of blood sugar, however, meta-analysis of the available RCTs is not available to guide decision making regarding the level of glucose at which different health benefits accrue and such studies may prove to be underpowered for this purpose. It is suggested that criteria are set at a level where there is an impact in RCTs not only on birth weight but outcomes including shoulder dystocia and Caesarean section.

A recent international consensus has suggested criteria which result in a diagnosis of gestational diabetes in 16-18% of the pregnant population, where all women are tested with 75 g OGTT.³⁷⁴ Women diagnosed using these criteria have a 1.75-fold increase in risk of macrosomia.^{330, 331} It is suggested that these international consensus criteria are adopted.

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Depending on individual clinical circumstance it is accepted that dietary intervention in women at lower glucose levels (two hour 7.8 to 8.5 mmol/l) may help to reduce birth weight, and dietary advice and intervention on an individual basis might be considered (for example, in previous macrosomia or previous complicated delivery).³³⁰

- ☑ The adoption of internationally agreed criteria for gestational diabetes using 75 g OGTT is recommended:
 - fasting venous plasma glucose ≥ 5.1 mmol/l, or
 - one hour value ≥ 10 mmol/l, or
 - two hours after OGTT ≥ 8.5 mmol/l.
- ☑ Women with frank diabetes by non-pregnant criteria (fasting venous glucose ≥ 7 mmol/l, two hour ≥ 11.1 mmol/l) should be managed within a multidisciplinary clinic as they may have type 1 or type 2 diabetes and be at risk of pregnancy outcomes similar to those of women with pre-gestational diabetes.

7.8.3 MANAGEMENT OF GDM

Management with dietary change to lower blood glucose levels and, if necessary, treatment with insulin improves outcomes in gestational diabetes.³³⁰ In one study, glycaemic management was tailored to control of preprandial and postprandial blood sugar.³³⁰ This study suggests that the majority of women with gestational diabetes (80%) can be managed with dietary therapy alone. If, after nutritional advice, preprandial and postprandial glucose levels are normal and there is no evidence of excessive fetal growth, the pregnancy can be managed as for a normal pregnancy.

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Two recent randomised controlled trials suggested that management strategies using metformin or glibenclamide can achieve similar outcomes to initial management with insulin although 20-40% of women will still eventually require insulin therapy.³⁷⁵⁻³⁷⁷ Metformin crosses the placenta and glibenclamide appears not to.^{375, 376}

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If blood glucose levels are in the range for established diabetes (see section 1.3), intensive specialist management and initial therapy with insulin is required.

A Pregnant women with GDM should be offered dietary advice and blood glucose monitoring and be treated with glucose-lowering therapy depending on fasting and postprandial targets.

- Glucose-lowering therapy should be considered in addition to diet where fasting or two hour glucose levels are above target, for example, where two or more values per fortnight are:
 - ≥ 5.5 mmol/l preprandial or ≥ 7 mmol/l two hours postprandial on monitoring at ≤ 35 weeks
 - ≥ 5.5 mmol/l preprandial or ≥ 8 mmol/l two hours postprandial on monitoring at > 35 weeks, or
 - any postprandial values are > 9 mmol/l.

B Metformin or glibenclamide may be considered as initial pharmacological, glucose-lowering treatment in women with gestational diabetes.

7.9 DELIVERY

National audit data in Scotland indicate that delivery in women with diabetes is generally expedited within 40 weeks gestation.^{311, 312} No clear evidence was identified to inform the optimal timing for delivery. The timing of delivery should be determined on an individual basis.

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Women who are at risk of pre-term delivery should receive antenatal corticosteroids.³⁷⁸ If corticosteroids are clinically indicated for pre-term labour, supervision by an experienced team is essential to regulate diabetic control.

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Women with diabetes have a higher rate of Caesarean section even after controlling for confounding factors.³⁷⁹

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- Women with diabetes requiring insulin or oral glucose-lowering medication who have pregnancies which are otherwise progressing normally should be assessed at 38 weeks gestation with delivery shortly after, and certainly by 40 weeks.
 - Women with diabetes should be delivered in consultant-led maternity units under the combined care of a physician with an interest in diabetes, obstetrician, and neonatologist.
 - Women with diabetes should have a mutually agreed written plan for insulin management at the time of delivery and immediately after.
 - 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.

7.10 INFANTS OF MOTHERS WITH DIABETES

Labour and delivery should only be undertaken in a maternity unit supported by neonatal intensive care facilities. 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

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Neonatal hypoglycaemia has been associated with adverse neurodevelopmental outcomes and impaired cognitive development.³⁸¹⁻³⁸⁶

A multicentre feeding study in preterm infants found significant hypoglycaemia (<2.6 mmol/l) was associated with reductions in Bayley motor and developmental scores of 13 and 14 points, respectively, at 18 months corrected age. An association between recurrent exposure to hypoglycaemia and a 3.5-fold increase in the incidence of cerebral palsy and developmental delay in infants was also found.³⁸⁴ However, methods of glycaemic monitoring and interventions were not standardised in the study, so caution is required before extrapolating these findings to term infants. Recurrent episodes of blood glucose <2.6 mmol/l in small for gestational age (SGA) pre-term infants were associated with measurable neurodevelopmental deficits, affecting fine motor ability and perceptual performance, that were still apparent at five years of age.³⁸⁵ Repeated episodes of hypoglycaemia have also been shown to produce a reduction in occipito-frontal head circumference (OFC), a surrogate marker of brain growth,³⁸⁷ at twelve, eighteen and sixty months of age.³⁸⁵

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

Glycaemic control at six weeks in women with type 1 diabetes, who exclusively breast fed, has been found to be significantly better than those who bottle fed.³⁸⁸ There are well documented health benefits for infants that are breast fed.

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

Although most medicines are not licensed for use in lactation, specialist reference sources provide information on suitability of medicines in breast feeding.^{325, 389, 390} Insulin, metformin and glibenclamide are considered compatible with breast feeding, although the infant should be observed for signs of hypoglycaemia.^{325, 389, 390} The antihypertensives commonly used in pregnancy: labetalol, nifedipine and methyldopa are found in breast milk in low concentration and these agents are considered appropriate for use in breastfeeding mothers, although with labetalol the infant should be monitored for bradycardia and hypotension.^{325, 389, 390} Of the ACE inhibitors, enalapril and captopril are considered safer.³⁹⁰ There is no information available on angiotensin-II receptor antagonists. Statins are not recommended in breast feeding.^{325, 389} Information on use of aspirin is conflicting with some sources advising low-dose aspirin is safe in breast feeding,³⁸⁹ while others advise cautious use due to potential for toxicity.³²⁵ Others do not recommend it due to potential risk of Reye's syndrome in the infant although amounts of aspirin in breast milk from antiplatelet doses will be very low.³⁹⁰

Specialist advice should be sought if the baby is premature or unwell.

7.11 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.

Breast feeding should be encouraged to benefit mother and baby but it may necessitate insulin dose adjustment and a dietetic review.

7.12 FOLLOW UP OF WOMEN WITH GDM

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

Rates of progression to type 2 diabetes in women with previous GDM vary widely (between 15 and 50% cumulative incidence at five years) and will be influenced by other risk factors such as ethnicity, obesity, and exercise.³⁹¹

A Cochrane review concluded that diet combined with exercise or diet alone enhances weight loss post-partum.³⁹² Both pharmacological and intensive lifestyle interventions reduce onset of type 2 diabetes in people with impaired glucose tolerance, including women with previous gestational diabetes.⁸⁷

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No robust evidence was identified to determine when follow-up testing should be carried out.

C Women who have developed GDM should be given diet, weight control and exercise advice.

C Women who have developed GDM should be reminded of the need for pre-conception counselling and appropriate testing to detect progression to type 2 diabetes.

- Where diabetes is not apparent immediately after delivery, glucose tolerance should be reassessed at least six weeks postpartum with a minimum of fasting glucose and with 75 g OGTT if clinically indicated.
 - An annual assessment of glycaemia using fasting glucose or HbA1c should be carried out thereafter.

7.13 CHECKLIST FOR PROVISION OF INFORMATION

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

Pre-pregnancy

- Discuss pregnancy planning with women with diabetes of childbearing age at their annual review.
- Advise women with diabetes who are planning pregnancy that they will be referred to a pre-pregnancy multidisciplinary clinic and outline the benefits of multidisciplinary management.
- Provide information on the risks of diabetes to both mother and fetus.
- Explain why a review of glycaemic control is necessary. Suggest that they should aim for HbA1c of <7% (53 mmol/mol) for three months prior to pregnancy.
- Advise that folic acid 5 mg (available on prescription only) should be taken for three months prior to conception and until the end of week 12 of pregnancy.
- Offer lifestyle advice, for example, on stopping smoking, alcohol consumption and exercise.
- Explain about the need for a review with the dietitian.
- Explain that a review of all medication will be necessary when planning a pregnancy and offer advice on which medications may need to be stopped, the reasons behind stopping and what the alternatives are.
- Provide contact telephone numbers.

Pregnancy

- Ensure that the principles of the Keeping Childbirth Natural and Dynamic (KCND) initiative are maintained where possible.
- Advise women with diabetes who are pregnant that they will be referred to a joint diabetes antenatal clinic (where available) and outline the benefits of multidisciplinary management.
- Explain that a review of all medication will be necessary when pregnant and offer advice on which medications may need to be stopped, the reasons behind stopping and the alternatives available.
- Advise women about the risks of hypoglycaemia, how to recognise the warning signs and symptoms and what treatment they may require. Ensure they have a glucagon kit and know how and when to use it.
- Advise that during pregnancy tight glycaemic control is necessary and they will need to monitor their blood glucose more often. Be clear about the targets that need to be achieved.
- Offer advice about sick day rules and planning for periods of illness (even minor) which may cause hyperglycaemia. These may include:
 - what to do with insulin or tablets
 - appropriate food to maintain blood glucose levels
 - how often to measure blood glucose and when to check for ketones
 - when to contact the diabetes team and contact numbers.
- Explain about the need for a review with the dietitian.
- Offer lifestyle advice, for example, on stopping smoking, alcohol consumption and exercise.
- Offer advice on safe driving and ensure that women inform the DVLA and their insurance company if they are starting on insulin.
- Inform women about the risk of retinopathy and advise that they will have retinal screening during each trimester. Explain what screening involves and what treatment to expect if retinopathy is found.
- Provide contact telephone numbers.

8 Management of diabetic cardiovascular disease

8.1 EPIDEMIOLOGY

Morbidity and mortality from cardiovascular disease (CVD) are two to five times higher in patients with diabetes compared with non-diabetics.³⁹³⁻³⁹⁹ 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.^{398, 400, 401} 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 socioeconomic 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.^{402, 403} There is an increased prevalence of cardiovascular disease in South Asian individuals with diabetes.^{398, 399}

8.2 CARDIOVASCULAR RISK FACTORS

8.2.1 DYSLIPIDAEMIA

Dyslipidaemia is commonly present in patients with type 2 diabetes.⁴⁰⁴ An increased concentration of LDL cholesterol or total cholesterol is an independent risk factor for cardiovascular morbidity and mortality.^{57, 58}

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The most common type of dyslipidaemia in type 2 diabetes is the combination of elevated triglycerides, low HDL and small, dense LDL.⁴⁰⁵ A 1 mmol/l reduction of LDL cholesterol represents a 21% reduction in risk of CVD.⁴⁰⁶

Triglycerides are an independent marker of increased risk of cardiovascular disease in type 2 diabetes.⁴⁰⁷

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8.2.2 HYPERTENSION

Hypertension is positively related to risk of CVD death, with a progressive increase in risk with rising systolic pressures.⁵⁷⁻⁵⁹ Each 10 mm Hg reduction in systolic pressure is associated with a 15% (95% CI 12 to 18%) reduction in the risk of CVD death over ten years.⁴⁰⁸

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8.2.3 HYPERGLYCAEMIA

Increasing glycaemia (measured as HbA1c) was associated with increased risk of CVD morbidity and mortality in observational data from UKPDS.⁵⁸ Each 1% (11 mmol/mol) lower HbA1c was associated with a 21% (95% CI 15 to 27%) lower risk of diabetes-related death and specifically a 14% lower risk of myocardial infarction (MI) over ten years. No lower threshold was demonstrated.⁴⁰⁹ Meta-analyses of RCTs suggest that intensive glycaemic control reduces the risk of cardiovascular disease by approximately 10% compared to standard care (with borderline statistical significance) but does not have a statistically significant effect on all-cause or cardiovascular disease mortality (see section 6.2.2).

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8.2.4 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 9), microalbuminuria is an independent marker associated with a doubling in cardiovascular risk.⁴¹⁰ There is insufficient evidence to determine whether reducing albumin excretion rate specifically reduces cardiovascular morbidity or mortality.

8.3 PRIMARY PREVENTION OF CORONARY HEART DISEASE

Risk estimation and the prevention of CVD is discussed fully in SIGN 97.⁷²

8.3.1 LIFESTYLE MODIFICATION

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

8.3.2 PHARMACOLOGICAL THERAPY

Glucose-lowering

For recommendations on glucose-lowering therapy for reducing cardiovascular risk in people with type 2 diabetes see section 6.

Antihypertensive therapy

Blood pressure (BP) lowering in people with diabetes reduces the risk of macrovascular and microvascular disease.^{6, 408, 409}

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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 the target group ≤ 90 mm Hg ($p=0.005$).⁴¹¹

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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.⁴¹² 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 of < 150 mm Hg. The long term follow up of these patients emphasised the need for maintenance of good blood pressure control.²⁴⁵ In an epidemiological analysis, lowest risk was observed in those with a systolic BP < 120 mm Hg.⁴⁰⁸

SIGN 97 recommends that the target systolic blood pressure for patients with diabetes should be < 130 mm Hg.⁷²

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D Target systolic blood pressure in people with diabetes is < 130 mm Hg.

When starting antihypertensive treatment, calcium channel blockers, diuretics and ACE inhibitors are equally effective. There was no significant difference in outcome among the three treatment groups in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).⁴¹³ A subgroup analysis of ALLHAT found an increase in heart failure in the patient group treated with alpha blocker as first line compared to a diuretic although this may simply reflect an increase in ankle swelling prevalence (RR of heart failure in patients with diabetes 1.85, 95% CI 1.05 to 2.55).⁴¹³

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The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) found that amlodipine (a calcium channel blocker) based treatment (with an ACE inhibitor as an add-on treatment) reduced the incidence of total cardiovascular events and procedures compared with an atenolol (beta blocker) regimen (with a thiazide diuretic as an add-on treatment) (HR 0.86, CI 0.76 to 0.98, $p=0.026$).⁴¹⁴ This study is also included in a meta-analysis of eight trials comparing beta blockers and other antihypertensive agents on cardiovascular outcomes which showed increased CV mortality in those treated with beta blockers in comparison with those treated with renin-angiotensin blockade agents.⁴¹⁵

There is evidence from two studies for the use of a combination of ACE inhibitor and diuretic. Compared to placebo, ACE inhibitor and diuretic in one study reduced blood pressure (5.6/2.2 mm Hg) and the relative risks of all deaths, cardiovascular deaths and major vascular events by 14% (p=0.025), 18% (p=0.027) and 9% (p=0.041) respectively, no matter the initial BP level.⁴¹⁶ A second study found that ACE inhibitor and diuretic reduced BP by 9.5/4.6 mm Hg compared to placebo. The reduction in risk of further stroke for those with diabetes was 38% (95% CI 8 to 58%) equivalent to one stroke avoided for every 16 patients treated for five years.⁴¹⁷

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Angiotensin-II receptor blockers (ARBs) are equally effective alternative antihypertensive agents in patients with ACE inhibitor-induced cough or rash.⁴¹⁸ They also have similar renal benefits in patients with microalbuminuria.⁴¹⁹

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The British Hypertension Society A/CD algorithm has been accepted as the best method of defining combination drug therapy. It specifies the use of ACE inhibitors (or ARBs if intolerant), calcium channel blockers and thiazide-type diuretics. The A/CD algorithm can be found in SIGN 97: Risk estimation and the prevention of cardiovascular disease.⁷²

A Patients with diabetes requiring antihypertensive treatment should be commenced on:

- an ACE inhibitor (ARB if ACE inhibitor intolerant), or
- a calcium channel blocker, or
- a thiazide diuretic.

A Beta blockers and alpha blockers should not normally be used in the initial management of blood pressure in patients with diabetes.

- An algorithm such as the A/CD should be followed, unless there is a specific indication that a particular specific class be used first (eg ACE inhibitor or ARB in those < 55 years or with nephropathy, beta blockers in ischaemic heart disease). The expectation should be that most patients end up on more than one agent.

Antiplatelet therapy

The role of aspirin in primary prevention remains uncertain. In the HOT study 75 mg of aspirin further reduced 'major cardiovascular events' in well controlled hypertensive patients with diabetes (HR 0.85, p=0.03).⁴¹¹ In this study non-fatal major bleeds were significantly more frequent among patients receiving aspirin (HR 1.8, p<0.001).

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In a Scottish population, there was no significant reduction in cardiovascular outcomes (HR 0.98, p=0.86) using 100 mg of aspirin compared to placebo.⁴²⁰ In a Japanese population, 81-100 mg of aspirin did not significantly reduce the primary outcome of cardiovascular disease (HR 0.80, p=0.16) in an open labelled study.⁴²¹

Further studies are underway.^{422, 423}

A meta-analysis of six RCTs (10,117 patients) found no statistically significant reduction in the risk of major cardiovascular events or all-cause mortality when aspirin was compared to placebo or no aspirin in people with diabetes and no pre-existing cardiovascular disease. Aspirin significantly reduced the risk of myocardial infarction in men (RR 0.57, 95% CI 0.34 to 0.94) but not in women (RR 1.08, 95% CI 0.71 to 1.65; p for interaction=0.056). Evidence relating to harms was inconsistent.⁴²⁴

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A Low-dose aspirin is not recommended for primary prevention of vascular disease in patients with diabetes.

Lipid lowering

Three large RCTs (CARDS, ASCOT, HPS) examined the effects of statins versus placebo in people with diabetes and no existing cardiovascular disease.⁴²⁵⁻⁴²⁷ The patients were male and female aged 40-80 years, with a small ethnic group, with baseline hypertension or other additional cardiovascular risk factors. One study (Collaborative Atorvastatin Diabetes Study, CARDS) included only patients with type 2 diabetes.⁴²⁵ A small number of people with type 1 diabetes were included in another study (Heart Protection Study, HPS).⁴²⁷ Statin therapy (atorvastatin 10 mg or simvastatin 40 mg) significantly reduced cardiovascular events comprising stroke, acute coronary events and coronary revascularisations (percutaneous coronary intervention, PCI, and coronary artery bypass grafting, CABG).

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The reduction of events in patients with type 1 diabetes did not differ from patients with type 2 diabetes but did not reach individual statistical significance. Reduction in cardiovascular events was seen regardless of baseline cholesterol concentrations. People with diabetes experienced no more side effects from statins compared to people without diabetes.⁴²⁷

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A Lipid-lowering drug therapy with simvastatin 40 mg or atorvastatin 10 mg is recommended for primary prevention in patients with type 2 diabetes aged > 40 years regardless of baseline cholesterol.

B Lipid-lowering drug therapy with simvastatin 40 mg should be considered for primary prevention in patients with type 1 diabetes aged > 40 years.

Patients under 40 years with type 1 or type 2 diabetes and other important risk factors, eg microalbuminuria, should be considered for primary prevention lipid-lowering drug therapy with simvastatin 40 mg.

8.4 MANAGEMENT OF PATIENTS WITH DIABETES AND ACUTE CORONARY SYNDROMES

SIGN 93 covers the management of acute coronary syndromes in the general population.⁴²⁸ Some evidence statements and recommendation from SIGN 93 have been reproduced here.

Unless covered specifically in the following sections, the principles of management are as for patients without diabetes.

Acute coronary syndromes are a common cause of death in people with diabetes. However, the case fatality from myocardial infarction is double that of the non-diabetic population.⁴²⁹

8.4.1 GLYCAEMIC CONTROL

Elevated blood glucose at hospital admission is a strong independent risk marker for patients with myocardial infarction.⁴³⁰ There have been two major RCTs investigating the effects of insulin and glucose infusion in diabetic patients with acute myocardial infarction. In the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial (n=620), intensive metabolic control using insulin and glucose infusion in patients with diabetes mellitus or a blood glucose > 11.0 mmol/l conferred a marked mortality benefit at one year (18.6% v 26.1%).⁴³¹ The subsequent DIGAMI 2 trial (n=1,253) investigated whether long term insulin therapy should be considered in patients with type 2 diabetes mellitus and acute myocardial infarction. It demonstrated that long term insulin was of no additional benefit, although there was extensive use of insulin at discharge in all treatment groups making interpretation difficult. For patients with type 2 diabetes mellitus, insulin is not required beyond the first 24 hours unless clinically required for the management of their diabetes.⁴³²

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B Patients with clinical myocardial infarction and diabetes mellitus or marked hyperglycaemia (> 11.0 mmol/l) should have immediate intensive blood glucose control. This should be continued for at least 24 hours.

8.4.2 PRIMARY CORONARY ANGIOPLASTY

Subgroup analysis has shown that primary angioplasty is equally successful in patients with and without diabetes, and may be more effective than thrombolytic therapy in patients with diabetes either with or without acute myocardial infarction.^{433, 434}

2+

A comprehensive systematic review and meta-analysis of RCT data showed that primary percutaneous coronary intervention is superior to thrombolysis for the treatment of patients with ST elevation acute coronary syndrome.^{435, 436} When compared with thrombolysis, primary PCI reduced short and long term mortality, stroke, re-infarction, recurrent ischaemia and the need for CABG surgery as well as the combined end point of death or non-fatal re-infarction. This benefit was consistent across all patient subgroups and was independent of the thrombolytic agent used. The greatest benefit was seen in those patients treated within 12 hours of symptom onset.^{435, 436}

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A Patients with an ST elevation acute coronary syndrome should be treated immediately with primary percutaneous coronary intervention.

8.4.3 THROMBOLYSIS

Thrombolytic therapy has been shown to reduce mortality after acute MI in patients 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 patients.⁴³⁷

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Compared with primary PCI, the benefit of thrombolysis on six month mortality is more time dependent and is associated with a lesser degree of myocardial salvage at all time points.^{438, 439} Evidence is lacking regarding the precise acceptable delay of primary PCI over thrombolysis. Considered expert opinion suggests that when primary PCI cannot be performed within 90 minutes of diagnosis, thrombolytic therapy should be administered.^{440, 441} This is based upon the assumptions that there is a 30 minute delay to the administration of thrombolysis and that the superiority of primary PCI is most clear when the time difference between administration of thrombolysis and balloon inflation is ≤ 60 minutes.

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D When primary percutaneous coronary intervention cannot be provided within 90 minutes of diagnosis, patients with an ST elevation acute coronary syndrome should receive immediate thrombolytic therapy.

8.4.4 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.⁴⁴²

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

In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, clopidogrel (75 mg daily) was administered for between three and 12 months (median nine months) after non-ST elevation acute coronary syndrome.⁴⁴³ Although the study was not powered to assess temporal effects, the clinical benefits were predominantly seen in the first three months of therapy.⁴⁴⁴ There were no differences in clinical outcome beyond three months,⁴⁴⁴ although bleeding risks with clopidogrel were consistently higher.⁴⁴⁵ Clopidogrel therapy reduced the primary composite end point of cardiovascular death, myocardial infarction or stroke but this was principally driven by a reduction in recurrent non-fatal myocardial infarction. There was no demonstrable effect on mortality.

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The CURE trial specifically targeted recruiting centres with no routine policy for the early use of invasive procedures. Since this trial, routine clinical practice has moved to the more widespread invasive investigation of all medium-to-high risk patients to reduce the incidence of recurrent myocardial infarction. The benefits of clopidogrel therapy are likely to be overestimated in the modern era of interventional practice.

In the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial, long term combination aspirin and clopidogrel therapy (median follow up 28 months) demonstrated no additional benefit in comparison to aspirin alone.⁴⁴⁶ There appeared to be a modest benefit in the subgroup of patients with clinically evident atherosclerotic disease that included approximately 30% of patients with a history of myocardial infarction within the previous five years. The magnitude of this apparent benefit was similar to that seen in the CURE trial beyond three months from the index event.

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In the Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study (COMMIT/CCS-2), clopidogrel or placebo was administered with aspirin for up to four weeks (median 16 days) after ST elevation acute coronary syndrome.⁴⁴⁷ Patients prescribed clopidogrel had a reduced relative risk of death, re-infarction, or stroke compared with controls (OR 0.91, 95% CI 0.86 to 0.97, $p=0.002$).

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B In addition to long term aspirin, clopidogrel therapy should be continued for three months in patients with non-ST elevation acute coronary syndromes.

A In addition to long term aspirin, clopidogrel therapy should be continued for up to four weeks in patients with ST elevation acute coronary syndromes.

8.4.5 BETA BLOCKERS

Diabetes is not a contraindication to use of beta blockers, which reduce mortality, sudden cardiac death and re-infarction when given after acute myocardial infarction.⁴⁴⁸

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A meta-analysis of 25 RCTs involving over 20,000 patients on long term beta blocker therapy after myocardial infarction showed a 23% relative risk reduction in total mortality and a 32% relative risk reduction in sudden death.⁴⁴⁹ The Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial ($n=1,959$) in patients with low ejection fraction (<0.40) following myocardial infarction showed that delayed (3 to 14 days) and cautious uptitration (over 4 to 6 weeks post-infarction) of carvedilol resulted in a 3% absolute risk reduction (RR reduction 23%) in all-cause mortality compared with placebo. Although immediate beta blocker therapy should be avoided in patients with acute pulmonary oedema and acute left ventricular failure, subsequent cautious introduction of beta blockade is associated with major benefits.⁴⁵⁰

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A Patients with clinical myocardial infarction should be maintained on long term beta blocker therapy.

8.4.6 BLOCKERS OF THE RENIN ANGIOTENSIN SYSTEM

The major morbidity and mortality benefits of ACE inhibitor therapy have been widely established in patients with heart failure or with left ventricular dysfunction following myocardial infarction.^{451, 452}

Meta-analysis of almost 100,000 patients receiving therapy with a converting enzyme inhibitor within 36 hours of acute myocardial infarction and continued for at least four weeks, confirmed that ACE inhibitors reduced mortality and that most of the benefits appeared to occur during the first few days, when mortality was highest. Patients at higher risk appeared to obtain a greater absolute benefit.⁴⁵³

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A Patients with clinical myocardial infarction should be commenced on long term ACE inhibitor therapy within the first 36 hours.

8.4.7 LIPID LOWERING

Statin therapy in people with diabetes appears to be associated with a statistically significant reduction in the relative risk of various clinical end points including all-cause mortality and fatal and non-fatal MI.⁴⁵⁴

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A small number of RCTs which compared low-dose versus high-dose statins produced subgroup analyses of patients with diabetes. None of these studies adopted a treat to target approach. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) study atorvastatin 80 mg was compared with pravastatin 40 mg in patients who had been admitted with acute coronary syndromes.^{455, 456} In people with diabetes the use of atorvastatin 80 mg was associated with a significant reduction in a triple end point of death, MI and unstable angina.⁴⁵⁷ In the Treating to New Targets (TNT) study atorvastatin 80 mg was compared with atorvastatin 10 mg in patients with previous myocardial infarction, objective evidence of coronary heart disease or previous coronary revascularisation procedures.^{458, 459} In people with diabetes the use of atorvastatin 80 mg was associated with a significant reduction in major cardiovascular events (25% RR reduction in CHD death, MI, cardiac arrest or stroke; $p=0.026$).⁴⁶⁰ A marked reduction in cardiovascular events was particularly demonstrated in diabetic patients with CKD.⁴⁶¹ The main side effect in both studies was an increase in abnormalities of liver function tests.

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A Intensive lipid-lowering therapy with atorvastatin 80 mg should be considered for patients with diabetes and acute coronary syndromes, objective evidence of coronary heart disease on angiography or following coronary revascularisation procedures.

Two large RCTs of fibrate use in patients with known coronary heart disease were identified.^{462, 463} In the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) 2,531 patients with diabetes were randomised to gemfibrozil or placebo.⁴⁶² Gemfibrozil reduced the primary end point of non-fatal MI or cardiovascular death (RR reduction 22%, AR reduction 4.4%, $p=0.006$). Stroke and transient ischaemic attack were reduced by 31% and 59% respectively ($p<0.001$). Patients were not on baseline standard statin therapy. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study randomised 9,795 patients with diabetes to fenofibrate or placebo.⁴⁶³ The primary end point of coronary events was not reduced. A prespecified outcome measure of total cardiovascular events was reduced (RR reduction 11%, AR reduction 1%, $p=0.035$). Patients were not on baseline standard statin therapy.

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Whether or not fibrates improve cardiovascular outcome in patients without cardiac disease has been addressed by one RCT of 4,081 patients with diabetes randomised to gemfibrozil or placebo.⁴⁶⁴ The incidence of fatal and non-fatal infarction and cardiac death was reduced (RR reduction 34%, AR reduction 1.4%, $p<0.02$). Patients were not on baseline standard statin therapy.

There is insufficient evidence to recommend fibrates, ezetimibe or nicotinic acid for the primary or secondary prevention of cardiovascular outcomes in patients with type 1 or 2 diabetes treated with statins.

B Fibrate treatment can be considered in patients who are intolerant of statins.

8.5 MANAGEMENT OF PATIENTS WITH DIABETES AND HEART FAILURE

The management of chronic heart failure is discussed fully in SIGN 95.⁴⁶⁵ Some evidence statements and recommendations from SIGN 95 have been reproduced here.

Unless covered specifically in the following sections, the principles of management are as for patients without diabetes.

8.5.1 GLYCAEMIC CONTROL

Metformin

A meta-analysis addressing whether or not metformin increased or decreased mortality found no RCTs comparing metformin to placebo in patients with heart failure and diabetes.²⁵² In the observational studies identified, metformin is associated with a reduction in all-cause mortality (OR 0.85; CI 0.76 to 0.95; $p=0.004$).²⁵² Metformin has been associated with a reduction in readmission due to heart failure in observational studies.²⁵² Metformin is no longer contraindicated in patients with heart failure and diabetes.

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No evidence was identified on the effect of metformin on hospitalisation due to stroke or myocardial infarction.

Sulphonylureas

A meta-analysis addressing whether or not sulphonylureas increase or reduce mortality in patients with heart failure and diabetes found too little data to draw a conclusion. No studies were identified on the effect of sulphonylureas on death or hospitalisation due to heart failure, MI or stroke.²⁵²

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Insulin

A meta-analysis addressing whether insulin increased or decreased mortality found no RCTs comparing insulin to placebo in patients with heart failure and diabetes.²⁵² In three included observational studies, insulin was associated with an increased mortality when compared to different hypoglycaemic agents, while in one study it was not.

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No studies addressing whether or not insulin increases or decreases hospitalisation due to heart failure, myocardial infarction or stroke were identified.

Thiazolidinediones

Two meta-analyses addressed whether or not TZDs increase or reduce total mortality or hospitalisation due to heart failure in patients with diabetes and HF.^{252, 266} Only one small RCT ($n=224$) of patients with NYHA class I or II was included in the meta-analyses. This did not show a significant increase in heart failure hospitalisation. In observational studies TZDs are associated with increased hospitalisation and readmission due to heart failure.²⁵² These observational studies have different comparators. There is insufficient evidence from these observational studies and single RCT to conclude whether TZDs increase or decrease mortality.^{252, 266} TZDs are contraindicated in patients with NYHA III or IV heart failure.^{252, 266}

1+
2+**Other agents**

No evidence was identified to address whether or not acarbose, DPP-4 inhibitors or GLP-1 analogues increase or reduce death or hospitalisation due to heart failure, MI or stroke in patients with diabetes mellitus and chronic heart failure.

8.5.2 BLOCKERS OF THE RENIN ANGIOTENSIN SYSTEM

In the large Studies of Left Ventricular Dysfunction (SOLVD), 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.^{466, 467}

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ACE inhibitors were first shown to be effective in heart failure in the 1980s. Since then, many RCTs have confirmed their benefit on mortality and morbidity, in patients with chronic heart failure,^{466, 467} left ventricular diastolic dysfunction (LVSD), heart failure or both after MI,⁴⁶⁸⁻⁴⁷⁰ and in patients with asymptomatic LVSD.⁴⁷¹

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Meta-analysis of these and other major trials (n = 7,105 patients) has shown that in patients with chronic heart failure, treatment with an ACE inhibitor reduces relative risk of mortality by 23% (OR 0.77, 95% CI 67 to 88; absolute risk reduction ARR 6.1%) and admission for heart failure is reduced by 35% (95% CI 26 to 43%; ARR 10.2%).⁴⁷² In a further meta-analysis in patients with LVSD, heart failure or both after MI, relative risk of mortality was reduced by 26% (95% CI 17 to 34%; ARR 5.7%) and hospital admission by 27% (95% CI 15 to 37%; AR reduction 3.6%).⁴⁷³

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A Angiotensin converting enzyme inhibitors should be considered in patients with all NYHA functional classes of heart failure due to left ventricular systolic dysfunction.

8.5.3 BETA BLOCKERS

Many RCTs have been undertaken with beta blockers in patients with heart failure. In the Cardiac Insufficiency Bisoprolol Study II (CIBIS II),⁴⁷⁴ Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF),⁴⁷⁵ and Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS)⁴⁷⁶ trials a consistent, approximately one third reduction in total mortality was seen with bisoprolol, extended release metoprolol succinate and carvedilol. In the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with heart failure (SENIORS) trial, nebivolol significantly reduced a composite outcome of death or cardiovascular hospitalisations in elderly heart failure patients.⁴⁷⁷

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There is consistent evidence for positive benefits from beta blockers in patients with heart failure, with risk of mortality from cardiovascular causes reduced by 29% (95% CI 14% to 42%); mortality due to pump failure reduced by 36% (95% CI 9% to 55%); and all-cause mortality reduced by 23% (95% CI 8% to 35%).⁴⁷⁸

Benefits were seen with beta blockers with different pharmacological properties, whether β 1 selective (bisoprolol, metoprolol, nebivolol) or non-selective (carvedilol).

Two formulations of metoprolol were used in clinical trials of patients with chronic heart failure. Only long-acting metoprolol succinate has been shown to perform better than placebo in reducing mortality.⁴⁷⁵ Short-acting metoprolol tartrate, given twice daily, was compared to carvedilol in Carvedilol or Metoprolol European Trial (COMET).⁴⁷⁹ Carvedilol reduced mortality over five years by 17% compared with metoprolol tartrate (33.8% v 39.5%), (HR 0.83, 95% CI 0.74 to 0.93, ARR 5.7%, p=0.0017).

1+

Beta blockers produce benefit in the medium to long term. In the short term they can produce decompensation with worsening of heart failure and hypotension. They should be initiated at low dose and only gradually increased with monitoring up to the target dose. Beta blockers are contraindicated in patients with asthma, second or third degree atrioventricular heart block or symptomatic hypotension and should be used with caution in those with low initial blood pressure (ie systolic BP < 90 mm Hg). There is some evidence that cardioselective beta blockers can be used safely in patients with chronic obstructive pulmonary disease (COPD) and heart failure.⁴⁸⁰

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A meta-analysis confirms that beta blockers also reduce mortality in diabetic patients with heart failure (RR 0.84, 95% CI 0.73% to 0.96%, p=0.011).⁴⁸¹

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A All patients with heart failure due to left ventricular systolic dysfunction of all NYHA functional classes should be started on beta blocker therapy as soon as their condition is stable (unless contraindicated by a history of asthma, heart block or symptomatic hypotension).

8.6 MANAGEMENT OF PATIENTS WITH DIABETES AND STABLE ANGINA

The management of stable angina is discussed fully in SIGN 96.⁴⁸² Some evidence statements and recommendations from SIGN 96 have been reproduced here.

Unless covered specifically in the following sections, the principles of management are as for patients without diabetes.

Patients with angina due to CHD are at risk of cardiovascular events and are eligible for secondary preventative treatments to lower their risk of CVD. These interventions are considered in more detail in SIGN guideline 97 on risk estimation and the prevention of cardiovascular disease.⁷²

8.6.1 ANTIPLATELET THERAPY

Evidence from 287 studies involving a total of 135,000 patients with cardiovascular disease including stable angina has shown that antiplatelet therapy, mainly with aspirin, given in a dose ranging from 75 to 150 mg daily led to a significant reduction in serious vascular events, non-fatal myocardial infarction, non-fatal stroke and vascular mortality.⁴⁴²

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Enteric-coated products do not prevent the major gastrointestinal complications of aspirin therapy and are significantly more expensive than the standard dispersible formulation.⁴⁸³⁻⁴⁸⁵

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8.6.2 LIPID LOWERING WITH STATINS

A meta-analysis of data from 14 randomised trials of statins involving 90,056 patients including patients with stable angina has shown the overall benefit of statin therapy. There was a significant reduction in all-cause and coronary mortality, myocardial infarction, the need for coronary revascularisation and fatal or non-fatal stroke.⁴⁸⁶

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A All patients with stable angina due to atherosclerotic disease should receive long term standard aspirin and statin therapy.

8.6.3 BLOCKERS OF THE RENIN ANGIOTENSIN SYSTEM

The HOPE study involved 9,297 high-risk patients with vascular disease or diabetes plus one other cardiovascular risk factor without history of heart failure or left ventricular dysfunction.⁴⁸⁷ 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 to 36%, $p=0.0004$).

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The use of perindopril in the European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) study involving 13,655 patients with stable coronary disease and no clinical evidence of heart failure reduced the risk of cardiovascular death, myocardial infarction or cardiac arrest.⁴⁸⁸ This significant reduction in cardiovascular events is mainly due to the reduction in the incidence of non-fatal myocardial infarction. Unlike the HOPE study, the effect on all-cause mortality did not reach a statistically significant level. Subgroup analysis of the trial showed that benefit from perindopril is mainly in patients with a history of myocardial infarction.

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Two other trials of ACE inhibitors did not show any benefit in patients with stable coronary heart disease. The Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial of trandolopril in 8,290 patients with no history of clinical heart failure or echocardiographic evidence of left ventricular systolic dysfunction did not reveal any benefit on cardiovascular events although the event rate was unexpectedly low.⁴⁸⁹ The study population in this trial was of lower risk and received more intensive treatment of risk factors than did those in the HOPE and EUROPA trials.

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A smaller trial (Quinapril Ischemic Event Trial, QUIET) of 1,750 patients with coronary heart disease and normal left ventricular function found that the ACE inhibitor quinapril did not significantly affect clinical outcomes or the progression of coronary atherosclerosis.⁴⁹⁰ All patients recruited to this trial had undergone successful coronary angioplasty involving the revascularisation of at least one coronary artery.

A meta-analysis of six randomised trials, including 33,500 patients with coronary artery disease and preserved left ventricular systolic function showed that ACE inhibitors significantly reduced cardiovascular (RR 0.83, CI 0.72 to 0.96; ARR 0.86%, p=0.01) and all-cause mortality (RR 0.87, CI 0.81 to 0.94; ARR 1.06%, p=0.0003).⁴⁹¹

When the findings of the HOPE, EUROPA, and PEACE trials were combined in a meta-analysis of 29,805 patients, ACE inhibitors significantly reduced all-cause mortality (7.8 v 8.9%, p=0.0004), cardiovascular mortality (4.3 v 5.2%, p=0.0002), non-fatal myocardial infarction (5.3 v 6.4%, p=0.0001) and all stroke (2.2 v 2.8%, p=0.0004).⁴⁹² Although PEACE and QUIET, which did not show a benefit of ACE inhibitors among their populations, both recruited patients at apparently lower CVD risk, the PEACE trial was underpowered rather than affected by low cardiovascular event rates in the study population.

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Patients with left ventricular systolic dysfunction (LVSD) or heart failure are at higher risk than those included in HOPE, EUROPA or PEACE and will gain relatively more benefit from ACE inhibitor therapy.⁴⁹² Systematic reviews in patients with chronic heart failure or LVSD indicate absolute risk reductions ranging from 3.8 to 6%.^{452, 472} All patients with stable vascular disease are likely to derive some benefit from these drugs, to a degree approximately proportional to the level of baseline risk.

A All patients with stable angina should be considered for treatment with ACE inhibitors.

Other than a significant reduction in stroke events with losartan in patients with left ventricular hypertrophy,⁴⁹³ studies of angiotensin II receptor blockers have failed to show cardiovascular benefit on their own,⁴⁹⁴⁻⁴⁹⁶ or in combination with an ACE inhibitor.⁴⁹⁷

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8.6.4 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, for example 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 SIGN guideline 96 on the management of stable angina.⁴⁸²

The Bypass Angioplasty Revascularization Investigation (BARI) trial suggested that amongst patients with diabetes, 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.⁴⁹⁸ However, the more recent Emory Angioplasty vs Surgery Trial (EAST) reached similar conclusions.⁴⁹⁹ The American College of Cardiology/American Heart Association Task Force recommend CABG over PTCA in patients with multivessel disease.⁵⁰⁰

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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.⁵⁰¹ Platelet glycoprotein IIb/IIIa receptor antagonists (eg abciximab) also reduce mortality after angioplasty with or without stenting in patients with diabetes.⁵⁰²⁻⁵⁰⁵

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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.

Three large meta-analyses and two smaller meta-analyses compared drug-eluting stents (DES) and bare metal stents (BMS) for revascularisation in patients with diabetes.⁵⁰⁶⁻⁵¹⁰ Two further meta-analyses compared paclitaxel- and sirolimus-eluting stents (PES and SES) in patients with diabetes.^{511, 512} DES reduces in-stent re-stenosis and target lesion revascularisation when compared to BMS. No consistent effect on MI or death was demonstrated. No difference in outcome was demonstrated when patients with diabetes were treated with SES compared to PES.

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There are few data comparing newer generation DES with PES and SES in patients with diabetes. Most of the studies included in the meta-analyses concern revascularisation of patients with diabetes and chronic stable coronary heart disease and non-ST elevation myocardial infarction.⁵⁰⁶⁻⁵¹⁰ There are limited data on patients with ST elevation myocardial infarction or saphenous vein grafts.

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A In patients with diabetes, DES are recommended as opposed to BMS in stable coronary heart disease or non-ST elevation myocardial infarction to reduce in-stent re-stenosis and target lesion revascularisation.

8.7 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. There is little evidence specific to people with diabetes (see the SIGN guideline on management of acute stroke, SIGN 108).⁵¹³ Management of stroke is similar to that in non-diabetic patients. Routine glucose control should be maintained. Rehydration and intravenous insulin may also be required.

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8.8 PERIPHERAL ARTERIAL DISEASE

The most common complications of peripheral arterial disease are lower limb ischaemia, gangrene and amputation. For guidance on management of peripheral arterial disease see SIGN 89.⁵¹⁴

8.9 CHECKLIST FOR PROVISION OF INFORMATION

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

Primary Prevention

Patients with diabetes who have no CVD but have one or more risk factor (see section 8.2) should be advised how this will affect the likelihood of their developing CVD.

Patients should be given information to help them recognise the following risk factors:

- smoking
- dyslipidaemia
- hypertension
- hyperglycaemia
- central obesity

and a plan made to help them reduce those which affect them.

- Certain risk factors can be lessened with changes to lifestyle and patients should be given all possible support by trained staff to enable them to stop smoking, improve diet and/or increase their physical activity level.
- Medication as well as lifestyle modification may be necessary. Patients should be advised that success will depend upon their agreeing to follow the prescribed treatment to lower their risk of CVD. They should also be made aware of any potential side effects of drugs.

Secondary treatment

- Patients with diabetes and new or established CVD should be offered treatment similar to all others with heart disease. The additional factor to be considered is to obtain and maintain good glycaemic control.
- Patients should be encouraged to take advantage of all cardiac rehabilitation programmes offered.
- If aspirin is prescribed, reassurance may be necessary that it is still an appropriate treatment for people who have established vascular disease.

9 Management of kidney disease in diabetes

This section of the guideline focuses on the detection, prevention, and management of kidney disease in people with diabetes. More detailed guidance on the investigation and management of chronic kidney disease may be found in SIGN 103, Diagnosis and management of chronic kidney disease.⁵¹⁵ The management of end-stage renal disease (ESRD) and renal replacement therapy (RRT) are not considered in this guideline.

9.1 DEFINITIONS

Diabetic kidney disease is usually classified, on the basis of the extent of urine protein excretion, as either microalbuminuria or nephropathy.

Microalbuminuria is defined by a rise in urinary albumin loss to between 30 and 300 mg/day. Timed urine collections may be inaccurate and therefore a urinary albumin/creatinine ratio (ACR) > 2.5 mg/mmol in men and > 3.5 mg/mmol in women is often used to define microalbuminuria. This is the earliest sign of diabetic kidney disease 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. An ACR > 30 mg/mmol in a spot urine sample is consistent with a diagnosis of diabetic nephropathy, providing other causes have been excluded. This represents a more severe and established form of renal disease and is more predictive of total mortality, cardiovascular mortality and morbidity and end-stage renal failure than microalbuminuria.

The presence of retinopathy has often been taken as a prerequisite for making a diagnosis of diabetic nephropathy, but nephropathy can occur in the absence of retinopathy. In a Danish study of 93 people with type 2 diabetes, persistent albuminuria and no retinopathy, 69% had diabetic nephropathy, 12% had glomerulonephritis and 18% had normal glomerular structure.⁵¹⁶

Glomerular filtration rate (GFR) is defined as the volume of plasma which is filtered by the glomeruli per unit time and is usually measured by estimating the rate of clearance of a substance from the plasma. Glomerular filtration rate varies with body size and conventionally is corrected to a body surface area (BSA) of 1.73 m², the average BSA of a population of young men and women studied in the mid-1920s.⁵¹⁷

The majority of the evidence considered in this section of the guideline relates to people who are presumed to have diabetic kidney disease, ie they have diabetes and some level of proteinuria, with or without a reduced GFR. In most individuals this diagnosis is made clinically, as biopsy may not alter management. Classic diabetic kidney disease is characterised by specific glomerular pathology. It is important to note that there are other reasons why an individual with diabetes may develop proteinuria and/or a declining GFR, notably hypertensive nephropathy and renovascular disease. In many individuals, kidney disease will be due to a combination of one or more of these factors, and people with diabetes may develop kidney disease for other reasons not related to diabetes.

With the advent of reporting of estimated GFR, there are increasing numbers of people being identified with a sustained low GFR. These individuals have *chronic* kidney disease (CKD), which may be classified as shown in Table 5, but in the absence of proteinuria they would not generally be classified as having *diabetic* kidney disease.

Table 5: Stratification of chronic kidney disease

Stage	Description	GFR (ml/min/1.73 m ²)
1*	Kidney damage with normal or raised GFR	≥ 90
2*	Kidney damage with mild decrease in GFR	60-89
3A	Moderately lowered GFR	45-59
3B		30-44
4	Severely lowered GFR	15-29
5	Kidney failure (end-stage renal disease)	< 15

Notes: *in order to diagnose stages 1 and 2 CKD, additional evidence of kidney damage must be present, eg proteinuria.

If proteinuria (24 hour urine > 1 g per day or urine PCR > 100 mg/mmol) is present the suffix P may be added.

Patients on dialysis are classified as stage 5D

The suffix T indicates patients with a functioning renal transplant (can be stages 1-5).

9.2 PREVALENCE AND PROGRESSION OF KIDNEY DISEASE IN DIABETES

There are no Scottish national data on the prevalence of kidney disease in people with diabetes. Estimates of prevalence from individual studies must be interpreted in the context of their patient population, such as levels of deprivation and the proportion of individuals from ethnic minorities. In a cross-sectional study of approximately 34,000 adults with diabetes in three primary care trusts (PCTs) in east London, the prevalence of CKD stages 3-5 was 18%. The populations of these PCTs are among the most deprived in the UK and over 50% of the population is non-White. Compared with Whites, CKD stage 3 was less common in South Asians (OR 0.80, 95% CI 0.73 to 0.88) and Blacks (OR 0.51, 95% CI 0.44 to 0.58), but CKD stages 4 and 5 were more common in south Asians (OR 1.52, 95% CI 1.24 to 1.85) and Blacks (OR 1.27, 95% CI 0.86 to 1.85).⁵¹⁸ In another study of 7,596 people with diabetes from Salford (96% Caucasian), CKD stages 1-2 was present in 9%, stage 3 CKD in 24.8% and stage 4-5 CKD in 2.7%.⁵¹⁹

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The racial differences in CKD are not simply accounted for by the increased risk and prevalence of diabetes in minority ethnic populations. The higher incidence of Stage 4 and 5 CKD in minority ethnic populations may, in part, reflect reduced access to health care and genetic differences between populations.⁵²⁰

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The number of patients with diabetes commencing RRT in Scotland is increasing. Data from the Scottish Renal Registry show that the number of patients with diabetes as the primary cause of CKD has risen from 67 in the cohort of patients commencing RRT in Scotland in 1980-84 (8%), to 516 in the cohort commencing treatment in 2000-2004 (18%).⁵²¹

4

9.2.1 MICROALBUMINURIA AND PROTEINURIA

A large RCT of patients with type 2 diabetes (UKPDS) reported the percentage with proteinuria and microalbuminuria at baseline (diagnosis) and during follow up over 15 years.⁵²² At diagnosis 12.8% had microalbuminuria and 2.1% had evidence of proteinuria. The proportions of individuals with microalbuminuria and proteinuria over 15 years of follow up, for participants in the conventional management arm of the study, are shown in Table 6.

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Table 6: Proteinuria and microalbuminuria in people with newly diagnosed type 2 diabetes measured over 15 year follow up.

Follow up (years)	Number	Microalbuminuria (%)	Proteinuria (%)
Baseline	994	12.8	2.1
3	1048	14.5	2.5
6	938	18.3	3.5
9	721	25.4	6.5
12	348	34.2	10.3
15	95	39.0	12.6

In people with type 1 diabetes the cumulative incidence of microalbuminuria at 30 years disease duration is approximately 40%.⁵²³⁻⁵²⁵ For microalbuminuric patients the relative risk of developing proteinuria is 9.3 compared to normoalbuminuric patients.⁵²⁶ Twenty five per cent of individuals who were in the conventional arm of the Diabetes Control and Complications Trial (DCCT) had proteinuria, elevated serum creatinine (>177 micromol/l) and/or were on renal replacement therapy after 30 years of diabetes.⁵²⁷

Remission of microalbuminuria may occur (see section 9.5.4) and so the presence of microalbuminuria does not imply an inexorable progression to nephropathy. There are data to suggest that there has been a decrease in the incidence of diabetic nephropathy in people with type 1 diabetes diagnosed more recently, with earlier aggressive blood pressure and glycaemic control.⁵²⁸

In the general population, an estimated GFR of less than 60 ml/min/1.73 m² is associated with an increased risk of the major adverse outcomes of CKD (impaired kidney function, progression to kidney failure and premature death from cardiovascular disease).⁵²⁹⁻⁵³²

There is a strong relationship between reduced GFR and mortality (both all-cause and cardiovascular) in people with diabetes. In one study of people with type 2 diabetes, the hazard ratios for all-cause mortality across different stages of estimated GFR (eGFR) (≥ 90 , 60-89, 30-59 and 15-29 ml/min/1.73 m²) were 1.00, 1.27, 2.34 and 9.82.⁵³³ Similar data have been reported in other studies in people with diabetes.⁵³⁴⁻⁵³⁶

Microalbuminuria is associated with an approximately twofold increase in cardiovascular morbidity and mortality.⁴¹⁰ The four year mortality of microalbuminuric type 2 patients is 32%, and 50% of proteinuric type 2 patients have died within 4 years.^{537, 538} When proteinuria and hypertension are present the standardised mortality ratio is increased fivefold in men and eightfold in women with type 2 diabetes and 11-fold in men and 18-fold in women with type 1 diabetes.⁵³⁹

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9.3 SCREENING FOR KIDNEY DISEASE IN DIABETES

9.3.1 PREDICTION EQUATIONS

Prediction equations improve the inverse correlation between serum creatinine and GFR by taking into account confounding variables such as age, sex, ethnic origin and body weight. The formula developed by Cockcroft and Gault to estimate creatinine clearance,⁵⁴⁰ and the four-variable formula derived from the Modification of Diet in Renal Disease (MDRD) study to estimate GFR,⁵⁴¹ are the most widely used of these prediction equations. The Cockcroft-Gault formula incorporates age, sex and weight in addition to creatinine, while the four-variable MDRD formula incorporates age, sex, and ethnicity, but not weight. The limitations of these equations are discussed in SIGN 103.⁵¹⁵

- eGFR should be assessed on an annual basis in people with diabetes. More frequent assessment may be necessary in adults with established CKD.

9.3.2 MICROALBUMINURIA

Microalbuminuria is the earliest, clinically detectable manifestation of classic diabetic kidney disease. Conventional urine dipstick testing cannot reliably be used to diagnose the presence or absence of microalbuminuria.

A meta-analysis of 10 studies in patients with diabetes showed excellent performance of ACR measurement compared with albumin excretion rate (AER) (ACR summary diagnostic odds ratio 45.8, 95% CI 28.5 to 73.4).⁵⁴² There is a daily variability in urinary albumin loss and so ACR is best measured on an early morning specimen of urine.⁵⁴³

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Urine albumin excretion may be temporarily increased by other factors, such as intercurrent illness and diabetic ketoacidosis.⁵⁴⁴ Therefore, it is usual to require multiple positive tests, usually two out of three over a period of months, before microalbuminuria is confirmed.

The literature is confusing in relation to the timing of commencing screening in young people with diabetes. Early microvascular abnormalities may occur before puberty, which then appears to accelerate these abnormalities.⁵⁴⁵ Age and puberty are reported without any strict definition. For clarity and simplicity the guideline development group suggests that screening for kidney disease should commence at 12 years of age in both boys and girls.

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B ACR should be used to screen for diabetic kidney disease.

C Young people with diabetes should have ACR tested annually from the age of 12 years.

ACR should be measured in a first-pass morning urine specimen once a year. ACR may be measured on a spot sample if a first-pass sample is not provided (but should be repeated on a first-pass specimen if abnormal). Microalbuminuria is confirmed if, in the absence of infection or overt proteinuria, two out of three specimens have an elevated ACR.

9.3.3 PROTEINURIA

Proteinuria is associated with cardiovascular and renal disease and is a predictor of end organ damage in patients with hypertension. Detection of an increase in protein excretion is known to have both diagnostic and prognostic value in the initial detection and confirmation of renal disease.⁵⁴⁶

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In evaluating the diagnostic accuracy of tests of proteinuria, measurement of protein (or albumin) excretion in a timed urine collection over 24 hours has been used as a reference standard.⁵⁴⁷

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Protein/creatinine ratio (PCR) measured in early morning or random urine samples correlates closely with 24 hour proteinuria⁵⁴⁸ and is at least as good as 24-hour urine protein estimation at predicting the rate of loss of GFR in patients with CKD.⁵⁴⁹

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In individuals with significant proteinuria, a PCR on a first-pass morning urine specimen is preferable to a timed collection.

Annex 3 explains the relationship between urinary protein (and albumin) concentrations expressed as a ratio to creatinine and other common expressions of their concentration.

9.4 INVESTIGATION OF KIDNEY DISEASE IN DIABETES

There are no high quality studies to inform best practice in the evaluation and investigation of people with diabetes who have kidney disease and the decision to perform ultrasonography and a renal autoantibody screen should be made on an individual basis. Non-diabetic kidney disease should be suspected in any of the following circumstances:

- blood pressure is particularly high or resistant to treatment
- the person previously had a documented normal ACR and rapidly develops heavy proteinuria (ACR > 100 mg/mmol, or PCR > 70 mg/mmol)
- significant haematuria is present
- the GFR has worsened rapidly
- the person is systemically ill.⁵⁵⁰

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9.5 PREVENTION AND TREATMENT OF KIDNEY DISEASE IN DIABETES

Risk factors for the development and progression of diabetic nephropathy include:

- hyperglycaemia
- raised blood pressure
- baseline urinary albumin excretion
- increasing age
- duration of diabetes
- smoking
- genetic predisposition
- raised cholesterol and triglyceride levels
- male sex.

9.5.1 GLYCAEMIC CONTROL

Randomised controlled trials indicate that intensive glycaemic management will reduce the development of diabetic kidney disease. In the DCCT, a reduction in mean HbA1c from 9.0% to 7.0% (75 to 53 mmol/mol) 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.⁶ In UKPDS a reduction in HbA1c from 7.9% to 7.0% (63 to 53 mmol/mol) was associated with a 24% reduction in microalbuminuria, (RR 0.76, 95% CI 0.53 to 0.88, $p < 0.001$) a 34% reduction in proteinuria (RR 0.66, 95% CI 0.39 to 1.1, $p = 0.036$) and a 74% reduction in the doubling of serum creatinine (RR 0.26, 95% CI 0.07 to 0.91, $p = 0.0028$) over 12 years in patients with type 2 diabetes.²⁴⁰

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Long term follow up of some of the individuals who participated in these studies has suggested that the benefits persist, even though glycaemic control in the intensive and control arms has converged in the post-trial period. In the follow up of the UKPDS study intensive glycaemic control with sulphonylurea or insulin therapy was associated with a relative risk reduction of 24% ($p = 0.001$) for microvascular disease after a median period of 16.8 years.²⁴⁵ There was no significant risk reduction in microvascular disease in the group treated with metformin compared to the conventional treatment group, but the number in the metformin group was small and underpowered to demonstrate such a difference in the post-trial follow-up period.

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After 30 years of type 1 diabetes, 9% of subjects in the intensive arm of the DCCT had developed nephropathy, as defined by either proteinuria, serum creatinine greater than 177 micromol/l and/or renal replacement therapy, compared with 25% in the conventional arm.⁵²⁷

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In the ADVANCE trial intensive glycaemic control (HbA1c 6.5% v 7.3% (48 to 56 mmol/mol)) in patients with type 2 diabetes was associated with a significant reduction in renal events, including new and worsening nephropathy (HR 0.79, 95% CI 0.66 to 0.93, $p = 0.006$) and new onset microalbuminuria (HR 0.91, 95% CI 0.85 to 0.98, $p = 0.02$).²⁴² All patients were treated with a sulphonylurea. This benefit was at the expense of significantly more severe hypoglycaemic events in the intensive group 2.7% v 1.5%.

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There are no studies specifically looking at whether sulphonylureas, metformin, sibutramine, rimonabant, exenatide, insulin or DPP-4 inhibitors have an additive benefit in reducing the development or progression of diabetic renal disease. There are limited data using the surrogate end point of reduction in proteinuria which suggests that thiazolidinediones may have an additive benefit over other hypoglycaemic agents in reducing proteinuria.⁵⁵¹⁻⁵⁵³

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The evidence for benefits of strict glycaemic control following development of microalbuminuria is limited. Among the patients with microalbuminuria in the DCCT, albumin excretion rate increased on average by 6.5% per year in the conventionally treated group compared to no change in the intensive group.⁶ In a study of 52 patients with type 2 diabetes and microalbuminuria, two years of improved glycaemic control (HbA1c 7.1% v 9.1% (54 v 96 mmol/mol)) resulted in stabilisation of urinary albumin excretion whereas albumin excretion rate tripled in the standard treatment group.⁵⁵⁴ In the VADT study of veterans with type 2 diabetes of whom 62% had microalbuminuria, intensive glycaemic control (HbA1c 6.9% v 8.4% (52 v 68 mmol/mol)) was not associated with a reduction in the development of overt nephropathy or doubling of serum creatinine.²⁴⁴

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Observational studies have reported a faster rate of progression of kidney disease in people with higher HbA1c.⁵⁵⁵ There are no RCTs suggesting that intensive glycaemic control slows down rate of progression of renal disease once overt proteinuria has occurred or when the glomerular filtration rate has fallen. This may indicate that the maximum benefit of intensive glycaemic control occurs when treatment is initiated at an earlier stage of the disease process. However, in pancreatic transplant recipients with evidence of diabetic kidney disease pre-transplant, histological improvements have been seen after 10 years of euglycaemia.⁵⁵⁶

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A Intensive glycaemic control in people with type 1 and 2 diabetes should be maintained to reduce the risk of developing diabetic kidney disease.

9.5.2 CONTROL OF PROTEINURIA

Post hoc analyses of two RCTs involving people with CKD and type 2 diabetes have shown that higher baseline proteinuria is associated with a higher risk of CKD progression.

One trial in 1,647 patients with type 2 diabetes with hypertension and CKD demonstrated a doubling of risk of progression to renal end points with each doubling of baseline proteinuria (HR 2.04, 95% CI 1.87 to 2.22).⁵⁵⁷ For each halving of proteinuria in the first year of follow up, the risk of ESRD at three years reduced by 56% (HR 0.44, 95% CI 0.40 to 0.49).

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Similarly, in an analysis of 1,513 people with type 2 diabetes with nephropathy, baseline proteinuria predicted long term outcome, eg comparing a baseline proteinuria of 3 g per gram of creatinine with 1.5 g per gram there was a relative risk of any renal end point of 5.2 and of ESRD of 8.1.⁵⁵⁸ The risk of ESRD shows a clear dependence on albuminuria reduction and on the residual level of albuminuria regardless of systolic blood pressure (SBP) change. However, the combination of albuminuria reduction with reduction in SBP produces the greatest risk reduction for ESRD.^{558, 559}

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One meta-analysis demonstrated that a reduction in proteinuria in response to antihypertensive treatment is reflected in a slower rate of GFR decline only in 'late' nephropathy.⁵⁶⁰ 'Late' is defined as the presence of overt proteinuria (0.5 g/per day or 0.3 g albuminuria/per day) and a GFR < 90 ml/min/1.73 m² (in people with type 1 diabetes) or < 75 ml/min/1.73 m² (in people with type 2 diabetes). The authors commented that the lack of a relationship between proteinuria reduction and GFR fall in 'early' nephropathy may reflect the reversibility of changes producing proteinuria at this stage.

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A Reducing proteinuria should be a treatment target regardless of baseline urinary protein excretion. However, patients with higher degrees of proteinuria benefit more. There should be no lower target as the greater the reduction from baseline urinary protein excretion, the greater the effect on slowing the rate of loss of GFR.

9.5.3 CONTROL OF BLOOD PRESSURE AND CKD PROGRESSION

Blood pressure lowering is associated with a reduced rate of CKD progression

Blood pressure (BP) reduction, proteinuria reduction and antihypertensive drug use are intrinsically linked in studies. An intervention is necessary to reduce BP or proteinuria, and this is generally an angiotensin converting enzyme (ACE) inhibitor, an angiotensin receptor blocker (ARB) or a non-dihydropyridine calcium channel blocker (CCB). Hence the papers included sub-analysed data to look for BP effects independent of the drugs used.

One very large meta-analysis has demonstrated a clear and large effect of BP reduction on slowing the progression of CKD. In this meta-analysis of 20 RCTs including over 50,000 patients with CKD (both diabetic and non-diabetic), the risk of ESRD reduced with each tertile of BP control, independent of the agent used. The group with the highest tertile of BP reduction, -6.9 mm Hg (-9.1 to -4.8), had a relative risk of ESRD of 0.74 (0.59 to 0.92).⁵⁶¹

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Subsequent data from a large RCT affirmed that antihypertensive therapy reduces the risk of renal disease irrespective of blood pressure at entry, and with no evidence of a threshold effect, ie the lowest risk for renal events was observed in those with a median achieved systolic blood pressure of 106 mm Hg.⁵⁶²

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Blood pressure lowering reduces proteinuria

One meta-analysis of 55 RCTs (n=5,714) in patients with CKD (with and without diabetes) according to tertile of BP reduction demonstrates a clear association between reduction in BP and reduction in albuminuria.⁵⁶¹ Additionally, in people with type 2 diabetes, post hoc analysis of the IDNT trial in 1,647 patients (which was not included in the above meta-analysis), demonstrated that a 10% reduction in diastolic blood pressure reduced proteinuria by 13.7%.⁵⁵⁷

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In people with diabetes and kidney disease, blood pressure should be reduced to the lowest achievable level to slow the rate of decline of glomerular filtration rate and reduce proteinuria.

9.5.4 ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS

Angiotensin converting enzyme inhibitors and ARBs confer both cardioprotective and renoprotective effects. ACE inhibitors and ARBs preferentially dilate the efferent renal arteriole reducing intraglomerular hypertension and reducing proteinuria independent of systemic blood pressure effects.

Prevention of microalbuminuria

One meta-analysis of 16 trials (7,603 patients) demonstrated that ACE inhibitors prevented the development of diabetic kidney disease in patients with no microalbuminuria (albumin excretion <30 mg/day) at baseline.⁵⁶³ This effect appeared to be present in patients with or without hypertension, patients with type 1 or type 2 diabetes, and patients with or without normal GFR.

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However, subsequent RCT data have questioned whether ACE inhibitors and ARBs prevent the development of microalbuminuria in normotensive people with type 1 and type 2 diabetes.^{564, 565} Further work is required in this area.

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Regression of microalbuminuria to no albuminuria

ACE inhibitors and ARBs can cause microalbuminuria to regress to no albuminuria in diabetes.^{566, 567} A meta-analysis of 36 RCTs (1,888 patients) demonstrated that ACE inhibitors increased the likelihood of regression from microalbuminuria to no albuminuria (RR 3.42, 95% CI 1.95 to 5.99) in patients with type 1 or 2 diabetes, both normotensive and with pre-existing hypertension. In patients with type 2 diabetes with hypertension, ARBs also increased the likelihood of regression from microalbuminuria to no albuminuria (RR 1.42, 95% CI 1.05 to 1.93), although this analysis did not correct for the BP lowering effects of these drugs.⁵⁶⁷ A smaller meta-analysis of 12 RCTs (689 patients) demonstrated an odds ratio for regression to no albuminuria of 3.07 (95% CI 2.15 to 4.44) for patients treated with ACE inhibitors; an effect attenuated but not abolished by adjusting for blood pressure, suggesting a specific antiproteinuric effect of these drugs.⁵⁶⁶

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Progression of microalbuminuria to macroalbuminuria

There is a reduction in the rate of progression of microalbuminuria to macroalbuminuria in patients with diabetes treated with ACE inhibitors or ARBs.⁵⁶⁶⁻⁵⁶⁸ A meta-analysis in patients with type 1 or type 2 diabetes in primary care demonstrated that ACE inhibitors (36 RCTs, 2,010 patients) reduced the rate of progression of micro- to macroalbuminuria by 45%, and ARBs (four RCTs, 761 patients, type 2 diabetes only) by 51% regardless of the presence or absence of baseline hypertension, diabetes type, or duration of treatment (ACE inhibitors, RR 0.55, 95% CI 0.28 to 0.71; ARBs, RR 0.49, 95% CI 0.32 to 1.05). ACE inhibitors and ARBs were not significantly different in their effects of progression of microalbuminuria. The analyses did not correct for the BP lowering effects of these drugs.⁵⁶⁷

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A meta-analysis of 12 RCTs in normotensive patients with type 1 diabetes (689 patients) demonstrated that the reduction in progression of micro- to macroalbuminuria (OR for progression 0.38, 95% CI 0.25 to 0.57) with ACE inhibitors was attenuated when blood pressure effects were adjusted for but not abolished suggesting a BP independent effect of ACE inhibitors on microalbuminuria.⁵⁶⁶

ACE inhibitors and ARBs reduce albuminuria in patients with diabetes⁵⁶⁹ and reduce proteinuria ranging from microalbuminuria to overt proteinuria (7.2 to 3,000 mg/day albuminuria). All the RCTs included had an active control arm in respect of BP. No difference in blood pressure was noted between the treatment groups to explain the reduction in albumin excretion rate.⁵⁶¹

Progression of CKD

In a meta-analysis of 36 RCTs in patients with type 1 or type 2 diabetes and CKD in primary care, the point estimate for developing ESRD or the doubling of serum creatinine was less in patients who were prescribed ACE inhibitors but not statistically significant (all cause mortality RR 0.64, 95% CI 0.40 to 1.03; doubling of serum creatinine RR 0.60, 0.35 to 1.05). This included the micro-HOPE study accounting for over half the patients in the analysis and which recruited patients with a high cardiovascular risk and mortality, but relatively low renal risk. This study alone produced opposite findings to the others in the meta-analysis (ie favoured placebo/no treatment), but, because of its size, accounted for 29% of the weighting of the overall result. Angiotensin receptor blockers did significantly reduce the risk of an adverse renal outcome in patients with type 2 diabetes (ESRD, RR 0.78, 95% CI 0.67 to 0.91; doubling of serum creatinine, RR 0.79, 95% CI 0.67 to 0.93).⁵⁶⁷

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A more recent meta-analysis of 24 studies compared the effects of ACE inhibitors or ARBs with placebo and/or a regimen not including a RAAS blocker on the incidence of ESRD, doubling of serum creatinine, or death from any cause in patients with diabetic nephropathy. Use of ACE inhibitors was associated with a trend toward reduction of ESRD incidence (RR 0.70, 95% CI 0.46 to 1.05) and use of ARBs with significant reduction of ESRD risk (RR 0.78, 95% CI 0.67 to 0.91). Both drug classes were associated with reduction in the risk of doubling of serum creatinine (RR 0.71, 95% CI 0.56 to 0.91 for ACEIs; and RR 0.79, 95% CI 0.68 to 0.91 for ARBs) but none affected all-cause mortality (RR 0.96, 95% CI 0.85 to 1.09 for ACEIs; and RR 0.99, 95% CI 0.85 to 1.16 for ARBs).⁵⁷⁰

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Combination treatment with ACE inhibitors and ARB

Two meta-analyses have looked at the effect of adding ARB treatment to ACE inhibitors in patients with CKD.^{571, 572} These show that combination treatment reduced proteinuria more than ACE inhibitors alone in both patients with diabetic and non-diabetic kidney disease. The role of blood pressure reduction in this effect is not clear.⁵⁷² The use of sub-maximal doses of the drugs limited the validity of conclusions.⁵⁷¹ Only one study in these meta-analyses studied the ability of the combination to slow CKD progression and suggested that the combination was better, but that trial has now been retracted.⁵⁷³ In one meta-analysis hyperkalaemia was increased overall by a small but significant amount (0.11 mmol/l, 95% CI 0.05 to 0.17 mmol/l).⁵⁷² In the other meta-analysis, clinically significant hyperkalaemia occurred in only 19 out of 434 patients, suggesting this is a safe combination, if monitored.⁵⁷¹

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In one RCT dual therapy with telmisartan and ramipril was compared with monotherapy in people with vascular disease or diabetes with end-organ damage.⁵⁷⁴ Most subjects had no diabetic kidney disease and so were at high cardiovascular risk, but low renal risk. Renal outcomes (dialysis, doubling of serum creatinine and death) were similar in the monotherapy arms (HR 1.00, 95% CI 0.92 to 1.09, NS) but increased in the combination therapy arm (HR 1.09, 1.01 to 1.18, $p=0.037$). It should be noted that the excess for dialysis in the combination was for acute renal failure and that the frequency of dialysis for CKD was similar in the three groups (although the study was not powered to show major differences in renal outcomes). By virtue of their baseline characteristics, the subjects in this study will have been at high risk of renovascular disease, which predisposes to acute renal failure both on initiation of treatment and in the case of another insult, eg volume depletion. Thus, use of combination treatment must take into account the general rule that therapy affecting the RAAS should be stopped when there is concurrent acute reduction in renal perfusion (see *SIGN 103 for further information*).⁵¹⁵

More data are required to determine the effect of combination therapy on disease progression before it will be possible to make a recommendation on this treatment.

A People with type 1 diabetes and microalbuminuria should be treated with an ACE inhibitor irrespective of blood pressure.

An ARB may be used if an individual with type 1 diabetes is intolerant of an ACE inhibitor.

A People with type 2 diabetes and microalbuminuria should be treated with an ACE inhibitor or an ARB irrespective of blood pressure.

A ACE inhibitors and/or ARBs should be used as agents of choice in patients with chronic kidney disease and proteinuria (≥ 0.5 g/day, approximately equivalent to a protein/creatinine ratio of 50 mg/mmol) to reduce the rate of progression of chronic kidney disease.

9.5.5 ALDOSTERONE ANTAGONISTS AND DIRECT RENIN INHIBITORS

One systematic review and several trials have examined the impact of mineralocorticoid receptor blocker (MRB) therapy (spironolactone or eplerenone) as additive therapy to conventional RAAS blockade in patients with CKD.^{575, 576} A majority of subjects studied had diabetic kidney disease, though individuals with $GFR < 30$ were excluded. In general, the trials were small, of short duration and poor methodological quality. Most trials demonstrated that spironolactone therapy reduced proteinuria (weighted mean reduction approximately 0.8 g/24 hours), but in a sub-analysis of four RCTs that included subjects with diabetic kidney disease, no significant reduction was identified.⁵⁷⁶ Spironolactone therapy was associated with a weighted mean reduction in blood pressure of approximately 3.4/1.8 mm Hg, but separate data on people with diabetes were not reported.⁵⁷⁶ Overall there was no effect on GFR, and no data were reported on doubling of serum creatinine, mortality, RRT, progression of microalbuminuria to macroalbuminuria or regression of macroalbuminuria to microalbuminuria.^{575, 576}

In one RCT of direct renin inhibition in 599 subjects with type 2 diabetes and nephropathy, aliskiren therapy combined with a maximal dose of losartan over a median period of six months was associated with a 20% reduction in mean ACR.⁵⁷⁷ There was a non-significant reduction in blood pressure of 2/1 mm Hg. No data were reported on mortality or long term renal outcomes. GFR reduction in the aliskiren group was 2.4 ml/min/1.73 m² v 3.8 ml/min/1.73 m² in the placebo group ($p=0.07$).

Both aliskiren and spironolactone have anti-proteinuric and anti-hypertensive effects, when given in combination with other drugs that block the RAAS, but there are insufficient data to support their routine use in diabetic individuals with kidney disease.

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9.5.6 RACIAL DIFFERENCES IN RENIN-ANGIOTENIN-ALDOSTERONE SYSTEM BLOCKADE

Renin-profiling studies have demonstrated that Caucasians have higher renin activity than Blacks of African descent and that consequently ACE inhibitors and ARBs tend to be more effective at lowering blood pressure in Caucasians.⁵⁷⁸ ACE inhibitor-associated cough may be more prevalent in individuals of Chinese origin.⁵⁷⁹ Most of the large RCTs on diabetic kidney disease have not reported race-specific outcomes, though in the Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with Angiotensin II Antagonist Losartan (RENAAL) trial, where 17% of participants were Asian, no effect of race on outcomes was reported.⁴⁹⁴

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Drugs that inhibit the renin-angiotensin-aldosterone system may be less efficacious in some racial groups.

9.5.7 LIPID LOWERING

Dyslipidaemia may contribute to the development and progression of diabetic kidney disease by causing intrarenal arteriosclerosis or direct toxicity to renal cells.^{580, 581} However, studies on the effect of lipid lowering on the development and progression of diabetic kidney disease are conflicting.

One observational study which included 197,551 subjects, 27% of whom had diabetes, reported that statins significantly reduced the odds of development of kidney disease as defined by doubling of the serum creatinine or an incremental rise in creatinine of 44 micromol/l (OR 0.87, 95% CI 0.82. to 0.92, $p < 0.0001$).⁵⁸²

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In a meta-analysis including 39,404 patients from 27 studies, statins reduced the rate of decline of GFR by 1.22 ml/min/year (95% CI 0.44 to 2.00 ml/min/year). However, in the subgroup analysis of patients with diabetes ($n = 122$) no benefit of statins on rate of progression or proteinuria was seen, although the authors concluded that larger studies were required to address this issue.⁵⁸³

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Two meta-analyses examined reduction in proteinuria with statin treatment. One demonstrated no significant change.⁵⁸³ The second meta-analysis included 1,384 patients in 15 studies, 57% of patients had diabetes. It demonstrated a significant reduction in microalbuminuria of 48% (95% CI 71% to 25%) and proteinuria of 47% (95% CI 67% to 26%).⁵⁸⁴ The effect was greatest with higher degrees of proteinuria.

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9.5.8 LIFESTYLE CHANGES

Diet

A more detailed discussion of dietary modification in chronic kidney disease is provided in SIGN 103.⁵¹⁵

Four small RCTs ($n = 69-131$) conducted in people with CKD stages 2-3 and diabetes (type 1 and type 2) did not demonstrate a beneficial effect of protein restriction (0.6 to 0.8 g/kg) on delaying disease progression.⁵⁸⁵⁻⁵⁸⁸ These studies followed up individuals for one to four years.

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For non-diabetic and diabetic patients with CKD stage 4, two systematic reviews and one meta-analysis suggested that, in comparison to other treatments, there was, at most, a modest benefit associated with restricting protein leading to a delay in CKD progression (0.53 ml/min/year, 95% CI 0.08 to 0.98 ml/min/year).⁵⁸⁹⁻⁵⁹¹

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In clinical practice any benefits of protein restriction have to be offset against the potential detrimental effects on nutritional status, the difficulties of patient compliance, potential effects on quality of life and the costs associated with implementation and monitoring.

It is not possible to deduce an optimal protein level from the available evidence. High protein intakes are associated with high phosphate intakes as foods that contain protein also tend to contain phosphate.⁵⁸⁷ It would appear prudent to avoid high protein intakes in stage 4 CKD patients when hyperphosphatemia is prevalent⁵⁸⁰ and this should be done under the guidance of an appropriately qualified dietitian.

A Dietary protein restrictions (<0.8 g/kg/day) are not recommended in patients with early stages of chronic kidney disease (stages 1-3).

High protein intake (>1.0 g/kg) is not recommended in patients with stage 4 chronic kidney disease.

Weight reduction and exercise

No evidence was identified that weight reduction or exercise affect the development or progression of diabetic kidney disease.

9.5.9 MULTIFACTORIAL INTERVENTION

In most individuals with diabetes, individual risk factors are not addressed in isolation. The benefits of a multifactorial approach in the management of people with type 2 diabetes and microalbuminuria have been clearly demonstrated.^{592, 593} The combination of improved glycaemic control, BP control, lipid lowering, aspirin, smoking cessation, exercise programmes and dietary intervention reduced the development of overt nephropathy at 3.8 years (RR 0.27, 95% CI 0.1 to 0.75, p=0.01) and the effect was maintained at 13.3 years, despite post-trial convergence between the two study groups, (RR 0.44, 95% CI 0.25 to 0.77, p=0.004). Only one person in the multifactorial intervention group required renal replacement therapy compared to six in the conventional treatment group (p=0.04).

1+

B People with diabetes and microalbuminuria should be treated with a multifactorial intervention approach.

9.6 MANAGEMENT OF COMPLICATIONS

9.6.1 ANAEMIA

Anaemia is a common finding in people with diabetic kidney disease and develops at an earlier stage compared to patients with chronic kidney disease from other causes. For a given eGFR patients with diabetic kidney disease have a haemoglobin level approximately 10 g/l less than patients with other causes of kidney disease. The prevalence of anaemia defined by the K/DOQI guidelines (haemoglobin <120 g/l for men and postmenopausal women and <110 g/l for premenopausal women) has been reported at 22-51% for patients with diabetic kidney disease compared to 8-14% in patients with other causes for chronic kidney disease.^{594, 595}

4

Anaemia should be investigated and managed as outlined in SIGN 103.⁵¹⁵

4

In a systematic review of 15 studies which focused on the treatment of the anaemia of CKD in pre-dialysis patients there was a significant improvement in quality of life on treatment with erythropoietin.⁵⁹⁶ This review included a meta-analysis of three small studies which showed no effect of treatment of anaemia on mortality (RR 0.60, 95% CI 0.13 to 2.88).

1+

The target haemoglobin in people with CKD and anaemia is not clear and adverse effects have been seen in people whose renal anaemia has been corrected to normal levels (see SIGN 103).⁵¹⁵ In a trial of darbepoetin alfa in 4,038 patients with diabetes, CKD and anaemia, there was no effect on the two primary composite outcomes of death or a cardiovascular event, or death or a renal event.⁵⁹⁷ The median achieved haemoglobin in the intervention group was 125 g/l and in the control group was 106 g/l. Individuals receiving darbepoetin alfa demonstrated a modest improvement in patient-reported fatigue, but had an increased risk of stroke (HR 1.92, 95% CI 1.38 to 2.68). Further studies are required to determine the optimum target haemoglobin in people with diabetes and CKD and the potential risks of such therapy need to be carefully balanced against quality of life benefits.

1+

D Patients with diabetes and CKD stage 3 -5 should have their haemoglobin checked at least annually.

A Erythropoiesis stimulating agents should be considered in all patients with anaemia of chronic kidney disease, including those with diabetic kidney disease.

9.6.2 RENAL BONE DISEASE

There is no evidence that renal bone disease occurs at a different stage in diabetic kidney disease than other causes of chronic kidney disease and monitoring should follow the recommendations in SIGN 103.⁵¹⁵

9.6.3 METABOLIC ACIDOSIS

There is no evidence that acidosis occurs at a different stage in diabetic renal disease than other causes of chronic kidney disease (see SIGN 103⁵¹⁵ for further discussion on the management of metabolic acidosis).

9.7 MODELS OF CARE

Two retrospective cohort studies suggested that referral to a combined diabetes-renal clinic was associated with better management of clinical variables associated with CKD and a slowing in decline of renal function. In one study the decline in GFR fell from 0.52 ml/min/month (in the first year) to 0.27 ml/min/month⁵⁹⁸ and in the other the decline in GFR fell from 1.09 ml/min/month (first year) to 0.39 ml/min/month.⁵⁹⁹

3

Two retrospective cohort studies demonstrated comparable benefits using different models of care – one was a nephrologist-led service,⁶⁰⁰ the other was a diabetologist-led clinic for patients with nephropathy.⁵⁹⁹ A common factor amongst all reports was that patients were managed intensively, using evidence based guidelines.

3

Investigation, monitoring and management of diabetic patients with mild to moderate kidney disease can be undertaken in a variety of settings, providing that appropriate expertise is available, there is a clear evidence based protocol, and facilities for intensive monitoring are available.

People with diabetes who are receiving dialysis require ongoing review of their diabetes. There may be ongoing issues regarding glycaemic control, such as symptomatic hyperglycaemia and recurrent hypoglycaemia which are usually best managed by diabetes healthcare professionals. Regular screening of eyes and feet are also essential given the high prevalence of sight-threatening retinopathy and foot disease in this patient group.

D **Individuals with diabetes and mild to moderate CKD should be managed in a setting that can provide appropriate investigation, monitoring and intensive clinical management.**

In situations where mild to moderate kidney disease is managed outwith a nephrology clinic, specific referral criteria should be agreed with the local nephrology services.

Whatever model of care is employed, a local evidence based protocol should underpin the clinical service.

Ongoing diabetes care is required for people with diabetes who are undergoing kidney dialysis.

9.8 CHECKLIST FOR PROVISION OF INFORMATION

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

- People with diabetes should be advised that kidney disease can occur as a complication of diabetes and that they should have an annual blood and urine test to screen for this.
- People with diabetes should be given information to help them recognise the following modifiable risk factors:
 - hypertension
 - hyperglycaemia
 - smoking
 - dyslipidaemia

and a plan made to help them reduce those which affect them.

- People with diabetes and kidney disease should be advised that they will usually require medication as well as lifestyle modification. They should be advised that success will depend upon their agreeing to follow the prescribed treatment to prevent progression of kidney disease. They should also be made aware of any potential side effects of drugs.

10 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.⁶⁰¹⁻⁶⁰³ However, with good care, visual impairment due to diabetes can be avoided for the vast majority of patients.

The majority of people with diabetes do not have any retinopathy. However, a minority have macular oedema or proliferative retinopathy that, untreated, may lead to visual impairment (sight-threatening retinopathy). Screening aims to refer to ophthalmology those people whose retinal images suggest they may be at increased risk of having, or at some point developing, sight-threatening retinopathy (referable retinopathy). When examined in ophthalmology, some of those referred will have sight-threatening retinopathy but many will just require regular ophthalmology review until they do develop sight-threatening retinopathy.

The diabetic retinopathy screening service was established to detect signs of diabetic retinopathy only. Patients should be aware of this and ensure that they continue to attend routinely to a community optometrist for all other eyecare needs (see section 10.2).

See section 7.6.3 for specific guidance on assessment and referral during pregnancy.

10.1 RISK IDENTIFICATION AND PREVENTION

10.1.1 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^{6, 604, 605}
- raised blood pressure⁶⁰⁶
- duration of diabetes^{607, 608}
- microalbuminuria and proteinuria^{609, 610}
- raised triglycerides and lowered haematocrit⁶¹¹
- pregnancy⁶¹²
- serum cholesterol for macular exudates and oedema.⁶¹³

1++
2+
3

A study examining lipids and development and progression of retinopathy concluded that total, HDL and LDL cholesterol levels predicted clinically significant macular oedema and hard exudate formation, but that there was no association of lipids with proliferative retinopathy or with retinopathy progression.⁶¹³

3

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

Diabetic retinal disease is the commonest cause of visual impairment in patients with type 1 diabetes, but not in type 2 diabetes.⁶¹⁴ Patients with diabetes have approximately a twofold increased risk of cataract^{615, 616} and the risk is increased with poor glycaemic control.⁶¹⁷ One study has indicated that intensive glycaemic control reduced the incidence of cataract extraction in people with type 2 diabetes.⁴⁰⁹

2++

The effect of smoking on the development and progression of retinopathy is unclear (see section 3.4).

10.1.2 RISK FACTOR MODIFICATIONS

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.^{522, 604, 618}

1++

Reducing HbA1c by 1.5% (16.4 mmol/mol) and, if possible, to 7% (53 mmol/mol) in type 1 and 2 diabetes^{522, 604} and reducing blood pressure to 144/82 mm Hg in type 2 diabetes reduces the incidence and progression of sight-threatening diabetic eye disease⁶⁰⁶ and this is likely also to be the case for type 1 diabetes. 1++

Reducing blood pressure and HbA1c below these targets is likely to reduce the risk of eye disease further.^{408, 409} Microvascular end points (including retinopathy) are decreased by 37% with each 1% (11 mmol/mol) reduction in HbA1c, and by 13% for each 10 mm Hg reduction in systolic blood pressure indicating that any improvement in these parameters is beneficial.^{409, 619} 2++

No evidence was identified suggesting that lowering blood pressure to a level < 130/75 mm Hg has a deleterious impact on retinopathy progression. One RCT highlights a subgroup of normotensive patients with type 2 diabetes in whom tight BP control (128/75 mm Hg) versus standard (137/81 mm Hg) reduced diabetic retinopathy (DR) progression over a follow-up period of 5.3 years⁶²⁰ (see section 8.3.2). 1++

A Good glycaemic control (HbA1c ideally around 7% or 53 mmol/mol) and blood pressure control (< 130/80 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 (see section 10.3.1).^{604, 621} 2++

B Laser photocoagulation, if required, should be completed before any rapid improvements in glycaemic control are achieved.

10.2 SCREENING

10.2.1 WHO SHOULD BE SCREENED?

The primary aim of screening is the detection of referable (potentially sight-threatening) retinopathy in asymptomatic people with diabetes so that treatment, where required, can be performed before visual impairment occurs. Screening is usually performed in the community using digital retinal photography. In this section screening is defined as the ongoing assessment of fundi with no diabetic retinopathy or non-sight-threatening diabetic retinopathy. Once sight-threatening eye disease develops treatment is usually required. This would normally be carried out in an ophthalmology clinic. Diabetic retinopathy screening does not obviate the need for a regular general eye examination to monitor changes in refraction and to detect other eye diseases.

Up to 39% of patients with type 2 diabetes have retinopathy at diagnosis, with 4-8% being sight threatening.^{522, 622} 1++

Screening for diabetic retinal disease is effective at detecting unrecognised sight-threatening retinopathy.^{623, 624} 2++
4

In patients with type 1 diabetes, pre-proliferative retinopathy has been identified 3.5 years after diagnosis in patients post-puberty and within two months of onset of puberty.⁶²⁵ 2+

In patients under 11 years old with type 1 diabetes, it takes five to six years for retinopathy to progress (relative risk of progression of retinopathy is 4.23 (95% CI 1.42 to 12.63, p=0.010). In patients aged 11 years or older with type 1 diabetes, it takes one to two years for retinopathy to progress (relative risk of progression of retinopathy is 1.39 (95% CI 1.15 to 1.72, p=0.003).⁶²⁶ A population based study demonstrated the prevalence of retinopathy to be 14.5% for any retinopathy and 2.3% for proliferative and pre-proliferative retinopathy in children and adolescents with insulin-dependent diabetes mellitus diagnosed before the age of 15 years (disease duration of < 12 years) and who were older than nine years at the time of examination.⁶²⁷ 2++
3

Fewer than 1% of patients with type 1 or type 2 diabetes and no retinopathy at baseline progress to referable retinopathy within two years compared to 1% within 0.3 years in those with background retinopathy at baseline.^{628,629,630} In patients with type 2 diabetes with no retinopathy but who are treated with insulin or have a duration of diagnosed diabetes > 20 years (or both) progression of retinopathy is faster.⁶³¹

2++
3

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

C Patients with type 1 diabetes should be screened from age 12 years.

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

- B**
- Patients with diabetes with no diabetic retinopathy could be screened every two years.
 - All others should be screened at least annually.

10.2.2 HOW SHOULD SCREENING BE PERFORMED?

Diabetes UK proposed 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%.⁶³² Some groups believe that visual acuity measurements help in the interpretation of maculopathy.⁶³³

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.⁶²³

2++

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 clinically significant macular oedema (CSMO).⁶³⁴⁻⁶³⁶

1+

One study, but with only small numbers of patients, suggested that wide angle scanning ophthalmoscopy could possibly be a useful tool for screening for macular oedema, although there was insufficient evidence to recommend its use.⁶³⁷

3

Between 3% and 14% of retinal photographs are ungradeable^{624, 638, 639} although this rate may be improved by digital imaging. Slit lamp biomicroscopy used by properly trained individuals can achieve sensitivities similar to,⁶²³ or greater than,⁶³⁶ retinal photography, with a lower technical failure rate. However, slit lamp biomicroscopy has only limited validation as a screening tool.⁶⁴⁰

2++

In patients attending ophthalmology units, optical coherence tomography (OCT) detects macular oedema with a sensitivity of 79% and a specificity of 88% compared to a reference standard of fundus stereo-photography or biomicroscopy.⁶⁴¹ There is insufficient evidence to recommend routine use of this tool at this time.

2++

Patients prefer screening to be performed at a site convenient to them.⁶⁴² Non-attendance at eye screening is associated with patients living in areas of social deprivation, those with poor glycaemic control, higher blood pressure, smokers, longer duration of diabetes and young people.⁶⁴³

2+

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

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

A ▪ clinically significant macular oedema

B ▪ proliferative diabetic retinopathy and severe non-proliferative diabetic retinopathy.

C Dilated direct ophthalmoscopy should only be used opportunistically.

- D** Screening modalities should aim to detect sight-threatening retinal disease with a sensitivity $\geq 80\%$ and specificity $\geq 95\%$.
- B** Patients with ungradeable retinal photographs should receive slit lamp and indirect ophthalmoscopy examination where possible.
- D** Screening should be performed at a site convenient to patients.
- Local strategies should be developed to encourage uptake of appointments, including promoting awareness of the service, the health benefits of attendance and risks of non-attendance.

10.2.3 GRADING AND QUALITY ASSURANCE

When grading retinal appearances, digital imaging is more sensitive than polaroid prints and probably similar to 35 mm film.⁶⁴⁴ Initial data indicate 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.⁶⁴⁵ 2+

An observational study suggested that an increase in the total number and area of haemorrhages and hard exudates temporal to the fovea is associated with the development of macular oedema.⁶⁴⁶ 2+

All screening modalities should undergo quality assurance checks. For retinal photography this should happen in 500 sets of images per grader per year.^{647, 648} 3
4

C Retinal photographs should be graded using digital images by an appropriately trained grader to facilitate quality assurance.

D All graders should have 500 retinal photographs rechecked for quality assurance each year.

One-field retinal photography has been shown to be as sensitive and specific as multiple-field photography for detecting referable retinopathy.^{639, 649} 2++

Automated grading can detect 'any retinopathy' on digital images with at-least-as-high sensitivity to manual screening when compared to a clinical reference standard.⁶⁵⁰ Automated grading can operate as the initial screener to exclude a majority of images with 'no retinopathy' before manual grading. The specificity of automated grading is less than manual grading, for equivalent sensitivity.⁶⁵⁰ 2++

Automated grading has a similar sensitivity for detecting referable retinopathy,^{650, 651} but may be less sensitive at detecting diabetic maculopathy.⁶⁴⁹ 2+
2++

B Either one field 45-50° retinal photography, or multiple field photography can be used for screening purposes.

B Automated grading may be used for distinguishing no retinopathy from any retinopathy in a screening programme providing validated software is used.

10.2.4 REFERRAL INTERVALS FOR DIAGNOSIS AND TREATMENT

Delay in treatment of more than two years from diagnosis of proliferative diabetic retinopathy is associated with poor outcome and severe visual loss.⁶⁵² When vitrectomy is required, a delay of over one year is associated with poorer visual outcome.⁶⁵³

1⁺⁺

A Scottish Government policy outlines intervals for all patients from referral to treatment.⁶⁵⁴

- All patients with referable retinopathy should be seen within 12 weeks.
- All patients with sight-threatening retinopathy should be treated within 18 weeks.
- Patients with high-risk proliferative retinopathy (neovascularisation of the disc or neovascularisation elsewhere with vitreous haemorrhage) should receive laser treatment urgently.

10.3 TREATMENT

10.3.1 LASER PHOTOCOAGULATION

Severe visual impairment (legal blindness) can be reduced through laser photocoagulation for people who have severe or very severe non-proliferative diabetic retinopathy, new vessels elsewhere with vitreous haemorrhage^{611, 633, 652, 655} and new vessels elsewhere without vitreous haemorrhage in people with type 2 diabetes.⁶⁵⁶

1⁺⁺
3
4

Macular laser using the Early Treatment Diabetic Retinopathy Study (ETDRS) modified grid can slow visual impairment in people with diabetes and macular oedema affecting the fovea in the absence of predominant macular ischaemia.^{634, 635, 657 658}

1⁺⁺
3

Although there are no clinical trial data assessing the effect of laser on preventing lesser levels of visual impairment or surgical intervention in people with type 1 diabetes and new vessels elsewhere it is common practice in the UK to offer laser photocoagulation.

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 people with type 1 or type 2 diabetes with new vessels at the disc or iris should receive laser photocoagulation.
 - Laser photocoagulation should also be provided for patients with new vessels elsewhere with vitreous haemorrhage.
 - All people with type 2 diabetes and new vessels elsewhere should receive laser photocoagulation.

D All people with type 1 diabetes with new vessels elsewhere should receive laser photocoagulation.

A Patients with severe or very severe non-proliferative diabetic retinopathy should receive close follow up or laser photocoagulation.

A Modified ETDRS grid laser photocoagulation should be used for patients with clinically significant macular oedema in the absence of significant macular ischaemia.

10.3.2 VITRECTOMY

Early vitrectomy is of proven value for improving long term vision in patients with type 1 diabetes and persistent vitreous haemorrhage. 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.⁶⁵⁹

1+

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

B Vitrectomy should be performed in patients with tractional retinal detachment threatening the macula and should be considered in patients with severe fibrovascular proliferation.

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

10.3.3 CATARACT EXTRACTIONS 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.^{660, 661} 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 or diabetic retinopathy following cataract extraction.^{660-662,663}

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.

10.3.4 PHARMACOLOGICAL THERAPY

Fenofibrate reduced the risk of progression of retinopathy and the need for laser treatment in patients with type 2 diabetes.^{463, 664} In this trial retinopathy was not the primary outcome, the outcomes were not explained by a change in the serum lipid profile and the effect was independent of its lipid-lowering properties.

1-

Intravitreal triamcinolone may provide a short term reduction in retinal thickness and a corresponding improvement in visual acuity.⁶⁶⁵⁻⁶⁶⁷ In the long term it does not appear to have any benefit over laser treatment.⁶⁶⁸⁻⁶⁷⁰ A small RCT showed that triamcinolone may be useful in patients who do not respond to laser, although in this trial there was a risk of raising intraocular pressure; 68% of patients were affected, with 44% requiring glaucoma medication and 54% of patients requiring cataract surgery.⁶⁷¹

1++

1+

One small RCT identified a non-statistically significant improvement in visual acuity and reduction in clinically significant macular oedema in patients on simvastatin.⁶⁷² A second small RCT of patients with type 2 diabetes and elevated serum lipids at baseline, found atorvastatin reduced the severity of hard exudates ($p=0.007$) post-laser, although the clinical significance of this is not certain.⁶⁷³

1+

Insufficient evidence was identified to warrant routine usage of anti-vascular endothelial growth factor (VEGF) therapies for the treatment of proliferative diabetic retinopathy or diabetic macular oedema either as stand-alone therapy or as an adjuvant to laser therapy. Phase II trials show a beneficial effect when used in combination with laser.^{674,675-679}

1+

1-

There is no good evidence for any additional benefit of ACE inhibitors in diabetic eye disease. In one multicentred RCT which addressed this issue, the baseline data were not well matched between control and ACE inhibitors groups and retinopathy was not a primary outcome for the study.⁶⁸⁰

In post hoc analysis of three RCTs which did not reach their primary end point, an ARB appeared to significantly reduce the incidence of new-onset retinopathy in patients with type 1 diabetes by 35% (HR 0.65, 95% CI 0.48 to 0.87) when measured as a change of three steps in the ETDRS scale, rather than the two steps in the original study design.^{681, 682} Treatment with an ARB enhanced regression of retinopathy by 34% (p = 0.009) in patients with type 2 diabetes.⁶⁸² These effects were only found in patients with early retinopathy.

Despite the initial Protein Kinase C Diabetic Retinopathy Study (PKC-DRS) showing a trend suggesting a beneficial effect on moderate visual loss, the follow-up PKC-DRS study showed that the progression to sight-threatening macular oedema was not significantly reduced. A subgroup analysis did indicate slower progression of diabetic macular oedema in the group treated with 32 mg ruboxistaurin (p = 0.4).^{683, 684} A further sub-analysis of data from the PKC-DRS study suggests that ruboxistaurin may slow visual acuity loss although this outcome was not a primary end point and was not prospectively defined.⁶⁸⁵

Although a number of treatments for diabetic retinopathy are of interest, there is no compelling evidence for their routine use.

10.4 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. Delay in registration can lead to reduced awareness of available disability benefits and support.⁶⁸⁶

Any level of visual impairment that results in a recognised disability for a patient will allow direct referral to a local low vision network and/or visual impairment team for assessment and ongoing support.

Low vision aid clinics⁶⁸⁷ and community self help groups^{688, 689} as part of a low vision service can improve the quality of life and functional ability for patients with visual impairment.^{690, 691}

D Community support, maximising disability benefits, 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 as soon as they fulfil the criteria.

10.5 CHECKLIST FOR PROVISION OF INFORMATION

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

Screening

When sent an appointment for screening, patients should be given the National Screening leaflet outlining:

- the screening procedure and the difference between screening and treatment
- the importance of early identification of retinopathy
- practical information relating to attendance and preparation for screening visits.

Referral to a specialist eye clinic

When invited to attend the eye clinic patients should be advised:

- to bring dark glasses as daylight may seem strong following dilation of the eye pupils
- that it will not be possible to drive a vehicle for around two hours, sometimes longer, following dilation
- there may be some discomfort following the eye drops and examination but it should pass in a few minutes.

At the end of the appointment the following should be discussed with the patient:

- the proposed course of action and any medication or treatment which may be involved
- self help advice relating to blood glucose control, diet and blood pressure
- advice that although changes have occurred these can be improved (depending on extent of change) and, if necessary, timely treatment can stop progression
- the interval for a follow-up appointment
- details of support services
- driving and DVLA regulations/restrictions.

Diagnosis as partially sighted or blind

- Patients should be advised of the process for visual impairment registration with the local social work department. This should be done as soon as possible after diagnosis so that benefits, assistance and assessment of support can be put in place.
- Advice should be provided on other local support services for emotional and family support as well as ongoing patient support, eg Royal National Institute for the Blind, Guide Dogs for the Blind, Citizens Advice Bureau, Council social work offices and support organisations for carers.
- Information on contacting the DVLA and insurance company should be provided.

11 Management of diabetic foot disease

11.1 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 patients without diabetes.⁶⁹²

Patients with diabetes are at increased risk of peripheral arterial disease (PAD), especially when other associated risk factors are present, for example smoking, hypertension and hypercholesterolaemia. Diabetic foot ulceration is principally associated with PAD and peripheral neuropathy, often in combination. Other factors associated with increased risk include previous amputation,⁶⁹³ previous ulceration,⁶⁹⁴ the presence of callus,⁶⁹⁵ joint deformity,⁶⁹⁶ visual/mobility problems⁶⁹⁷ and male sex.⁶⁹⁴ The cumulative effect of these risk factors is at least additive.⁶⁹⁶

11.2 RISK STRATIFICATION

Diabetic foot screening is effective in identifying the level of risk of developing foot ulceration in patients with diabetes.⁶⁹⁸⁻⁷⁰¹ A systematic review of 16 observational studies found that simple tests are effective at predicting those at risk of developing foot ulceration.⁶⁹⁸ Further studies found that risk stratification can identify those at increased risk of developing foot ulceration.⁷⁰⁰ Patients screened as being low risk have a 99.6% (95% CI 99.5 to 99.7%) chance of remaining free from ulceration (follow up at 1.7 years) and were 83 times less likely to ulcerate than the high-risk group.⁷⁶⁰

2++
2+
2-

Simple tests such as the use of 10 g monofilament, palpation of pulses, neuropathy disability score, presence of significant structural abnormality and previous ulceration, when routinely used during screening are effective at predicting ulceration.⁷⁰⁰ A neurothesiometer can be used as part of a more formal assessment to detect peripheral neuropathy, as can Doppler ultrasound to detect foot pulses. Ankle brachial pressure index can be used to assess for PAD, however it should be interpreted with caution in patients with diabetes as it is often falsely elevated.⁷⁰²

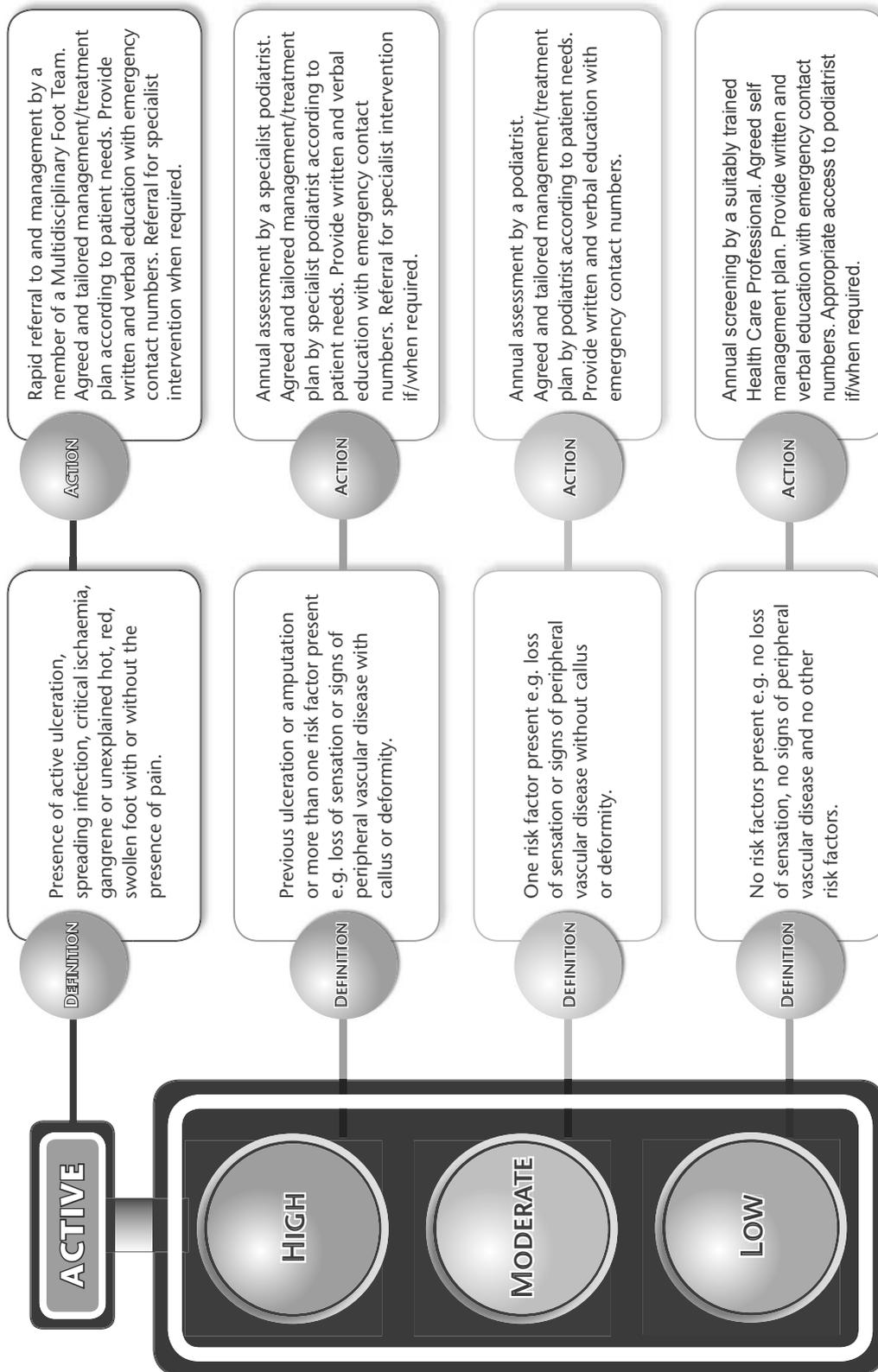
2++

B All patients with diabetes should be screened to assess their risk of developing a foot ulcer.

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

The result of a foot screening examination should be entered onto an online screening tool, such as SCI-DC, to provide automatic risk stratification and a recommended management plan, including patient information (see *Figure 1*).

DIABETIC FOOT RISK STRATIFICATION AND TRIAGE



These risk categories relate to the use of the SCL-DC foot risk stratification tool

Produced by the Scottish Diabetes Group - Foot Action Group

11.3 PATIENT EDUCATION

Several studies have assessed the role of foot education in patients with diabetes. Studies to date have been heterogeneous using different patient populations with small numbers and variable end points giving inconclusive findings. Previous work in this area indicated that at one year follow up, where patients had agreed 'personalised behavioural contracts', there was a significant reduction in serious lesions.⁷⁰³ A further study demonstrated little or no effect of a general education programme after 18 months follow up.⁷⁰⁴ 1+

A single RCT of patients with previous diabetic foot disease suggested that intensive education may be effective in the prevention of amputation or recurrent ulceration.⁷⁰⁵ 1+

Programmes which include education with podiatry show a positive effect on minor foot problems at relatively short follow up.^{706,707} Access to a podiatrist reduces the number and size of foot calluses and improves self care.⁷⁰⁷ 1+
2++

More recent studies assessing the effectiveness of structured education programmes for patients at high risk of diabetes-associated foot disease found an improvement in overall knowledge and foot care behaviours but no change in the incidence of foot ulceration or in amputation rates.^{24,708} 1+
1++

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

11.4 PREVENTATIVE FOOTWEAR AND ORTHOSES

Plantar pressure using ordinary shoes is similar to walking barefoot. Running-style, cushion-soled trainers can reduce plantar pressure more than ordinary shoes but not as much as custom-built shoes.^{709,710} 2++
3

There is limited evidence that padded hosiery can reduce peak plantar pressures.⁷¹¹

B Patients with diabetic foot disease should be advised to wear running-style, cushion-soled trainers rather than ordinary shoes.

The use of custom-made foot orthoses and prescription footwear reduces the plantar callus thickness and incidence of ulcer relapse.^{706,712-714} Patients who routinely wear their prescription shoes and orthoses are less likely to have ulcer relapse.⁷¹⁵ 1+
2+
3

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

11.5 MANAGEMENT OF ACTIVE FOOT DISEASE

11.5.1 MULTIDISCIPLINARY FOOT CLINIC

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.^{716-718, 719} Adherence to locally established protocols may reduce length of hospital stay and major complication rates.^{720, 721}

2+

A cohort study demonstrated that aggressive cardiovascular intervention in the multidisciplinary diabetic foot care clinic reduced mortality at five years by 38% in patients with neuroischaemia and 47% in patients with neuropathy ($p < 0.001$).⁷²²

2++

C Patients with active diabetic foot disease should be referred to a multidisciplinary diabetic foot care service.

A multidisciplinary foot team should include:

- podiatrist
- diabetes physician
- orthotist
- diabetes nurse specialist
- vascular surgeon
- orthopaedic surgeon
- radiologist.

A multidisciplinary foot service should address cardiovascular risk management.

11.5.2 DEBRIDEMENT

Evidence on local sharp debridement, surgical debridement, larvae therapy and hydrojet therapy proved insufficient to draw any conclusions. Clinical experience suggests that in an appropriate setting any of these methods of debridement are useful in the management of patients with diabetic foot disease. Local sharp debridement should be considered first followed by the others depending on the clinical presentation or response of a wound.

11.5.3 PRESSURE RELIEF

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 six weeks.⁷²³⁻⁷²⁵

1+

2+

Prefabricated walkers, when made irremovable, are a viable alternative to total contact casting.⁷²⁶⁻⁷²⁹ They are almost as good at reducing pressure, have similar ulcer healing rates (95% v 85%), are more cost effective and less time consuming.⁷²⁷

1+

1++

2++

A small study of 40 patients suggested that moderate weight bearing following plaster application is not detrimental.⁷³⁰

2++

Use of 'half shoes' reduces the time to complete closure of the ulcer to a mean of 10 weeks.⁷³¹

3

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

B Prefabricated walkers can be used as an alternative if they are rendered irremovable.

The walkers should be specially designed for use with the diabetic foot and should always incorporate a total contact insole.

11.5.4 ANTIBIOTIC THERAPY

No single broad spectrum antibiotic regimen was shown to be more effective over another in the treatment of patients with diabetic foot ulcers.⁷³²⁻⁷³⁴

1+

There is no evidence for the optimal duration or route of antibiotic therapy in the treatment of patients with diabetic foot ulcers. A consensus good practice guideline for the treatment of infected diabetic foot ulcers is available.⁷³⁵

- Treatment of a patient with an infected diabetic foot ulcer and/or osteomyelitis should be commenced immediately with an antibiotic in accordance with local or national protocols. Subsequent antibiotic regimens may be modified with reference to bacteriology and clinical response.

11.5.5 NEGATIVE PRESSURE WOUND THERAPY

In the treatment of active diabetic foot ulceration and postoperative wounds, several studies of variable methodological quality assessed the role of negative pressure wound therapy (NPWT) as an adjunct to standard wound care. Results from a systematic review of four RCTs of weak to moderate quality and a more recent RCT, the largest to date involving 342 patients, have suggested a benefit in using NPWT compared to advanced moist wound therapy.^{736, 737} NPWT appears to increase the proportion of patients who achieve complete ulcer closure (42.2% achieved complete ulcer closure with vacuum assisted closure/NWPT compared to 28.9% with standard dressings)⁷³⁶ and lowers the rate of secondary amputation (absolute risk reduction 7.9%).⁷³⁷

1+

- B** Negative pressure wound therapy should be considered in patients with active diabetic foot ulcers or postoperative wounds.

11.5.6 ARTERIAL RECONSTRUCTION

Patients with diabetes are more prone to PAD 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).⁷³⁸ Increased frequency of distal bypass is associated with reduced frequency of amputation.⁷³⁹⁻⁷⁴¹

2++

Infra-popliteal bypass surgery and angioplasty have similar reported limb salvage rates (around 80% at three years) in patients with critical limb ischaemia.^{742, 743} A single RCT has demonstrated broadly similar medium term results with a surgery-first approach and an angioplasty-first approach to infra-inguinal reconstruction.⁷⁴⁴

2++
1++

- B** All patients with critical limb ischaemia, including rest pain, ulceration and tissue loss, should be considered for arterial reconstruction.

11.5.7 CHARCOT NEUROARTHROPATHY OF THE FOOT

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

Clinical diagnosis of Charcot neuroarthropathy 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.⁷⁴⁵

2++

Acute Charcot neuroarthropathy is associated with a skin temperature 2 to 8°C higher than the contralateral foot as measured on thermography.^{746, 747}

3

Magnetic resonance imaging (MRI) cannot reliably distinguish acute Charcot neuroarthropathy from osteomyelitis. It does, however, provide additional information on boney involvement.

- C**
 - **Diagnosis of Charcot neuroarthropathy of the foot should be made by clinical examination.**
 - **Post-diagnosis thermography can be used to monitor disease activity.**

MRI can be used to detect early changes of Charcot neuroarthropathy which cannot be identified by X-ray.

Suspected Charcot neuroarthropathy of the foot is an emergency and should be referred immediately to the multidisciplinary foot team.

Treatment of patients with Charcot neuroarthropathy of the 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.⁷⁴⁷ One follow-up study showed that non-weight bearing and foot protection with therapeutic shoes resulted in a resolution rate of 96% in patients with diabetic foot deformities.⁷⁴⁶

3

- D** **Total contact casting and non-weight bearing are effective treatments for patients with acute Charcot neuroarthropathy of the foot.**

There is insufficient evidence to recommend the routine use of bisphosphonates in patients with acute Charcot neuroarthropathy of the foot, although case series involving small numbers of patients indicate that they may reduce skin temperature and bone turnover in active Charcot neuroarthropathy.^{748, 749}

11.6 PAINFUL DIABETIC NEUROPATHY

11.6.1 PHARMACOLOGICAL TREATMENT

There is good evidence that several agents can improve symptom control and quality of life in painful diabetic peripheral neuropathy (DPN). The evidence base for direct comparison of different agents is limited. Older generation tricyclic antidepressants (TCAs) amitriptyline, imipramine and desipramine are effective for the treatment of painful diabetic peripheral neuropathy (DPN).^{750, 751} More recent evidence has found that newer antidepressants can also be beneficial in DPN. Duloxetine has been shown to reduce pain intensity and improve quality of life. There appears to be no benefit in using higher doses as 60 mg was shown to be as effective as 120 mg/day.^{752, 753} Venlafaxine can also significantly reduce pain intensity although higher doses (150-225 mg) were required.^{754, 755} There was no increase in adverse effects with the higher dose.

1++

1+

Anticonvulsants such as carbamazepine and gabapentin have been shown to be more effective than placebo in reducing symptoms of painful DPN.^{750, 751, 756} Gabapentin is superior to placebo in patients with DPN and one RCT indicated it had fewer side effects than TCAs.⁷⁵⁶ Pregabalin is an effective agent for the treatment of patients with painful DPN.^{757, 758} Opiate analgesia in combination with gabapentin can improve symptom control in patients not controlled on monotherapy.^{757, 758}

1++

1+

The initial treatment of DPN is dependent on individual patient choice, dosing regimens, cost and side effect profile.

- A** **Antidepressants, including tricyclics, duloxetine and venlafaxine should be considered for the treatment of patients with painful DPN.**

- A** **Anticonvulsants, including pregabalin and gabapentin should be considered for the treatment of patients with painful DPN.**

- B** **Opiate analgesia in combination with gabapentin should be considered for the treatment of patients with painful DPN which cannot be controlled with monotherapy.**

11.6.2 NON-PHARMACOLOGICAL TREATMENT

No evidence was identified on the effectiveness of acupuncture, cognitive behavioural therapy, anodyne therapy or transcutaneous electrical nerve stimulator in the treatment of patients with painful DPN.

11.7 CHECKLIST FOR PROVISION OF INFORMATION

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

Screening

During annual foot screening patients should receive verbal and written advice on the following:

- how diabetes affects their feet
- why it is important to have foot screening and risk assessment
- how to care for their feet and when to seek help
- how to contact podiatry services within working hours
- what to do in an emergency out of hours
- patients should be offered NHSScotland leaflets on Low, Moderate or High Risk (available from www.sdsp.org.uk/patientleaflets). These leaflets should only be provided after screening and should be part of their management plan.
- other NHSScotland foot advice leaflets as appropriate, eg Footwear Advice Leaflet, Holiday Feet and Charcot Foot.

Treatment and management

Patients at high risk of ulceration or amputation, or who have previously had ulceration or amputation should be provided with a management plan prepared with their input. Those who present with no risk factors should be given advice regarding self care and self management.

Active foot disease

Patients with active foot ulceration should be referred to a multidisciplinary footcare service for the following advice and information:

- multidisciplinary footcare service emergency contact details
- emergency out of hours contact details
- risk factor modification, eg smoking cessation and good glycaemic control
- wound care and antibiotics, when required
- appropriate off loading
- complications as a result of therapy
- relevant patient support leaflets, eg Looking After Your Foot Ulcer, Charcot Foot.

12 Provision of information

This section reflects the issues likely to be of most concern to patients and their carers. These points are provided for use by health professionals when discussing diabetes with patients and carers and in guiding the production of locally produced information materials.

12.1 SOURCES OF FURTHER INFORMATION

12.1.1 NATIONAL ORGANISATIONS

Diabetes Information Plus

www.diabetesinfoplus.scot.nhs.uk

Provides access to diabetes information leaflets, and information on diabetes support groups, social security benefits, medicines and treatments and the evidence on which treatments are based.

Diabetes in Scotland

www.diabetesinscotland.org.uk

Diabetes UK (Scottish office)

The Venlaw, 349 Bath Street, Glasgow, G2 4AA

Tel: 0141 245 6380 • Careline 0845 120 2960

www.diabetes.org.uk • Email: Scotland@diabetes.org.uk

Diabetes UK provides a range of information on diabetes including leaflets, fact sheets and Diabetes UK's magazine Balance. They provide advice on all aspects of diabetes including diabetic care, diet, holidays and insurance.

Driver and Vehicle Licensing Agency

www.dft.gov.uk/dvla/medical.aspx

Healthtalkonline

www.healthtalkonline.org

Healthtalk online is the website of the DIPEX charity. It provides access to people's experiences of living with diabetes.

Juvenile Diabetes Research Foundation

Suite 5, 2nd Floor, Salvesen Tower, Blaikies Quay, Aberdeen, AB11 5PW

Tel: 01224 582777

www.jdrf.org.uk • Email: info@jdrf.org.uk

Provides a range of information and support to families and individuals affected by type 1 diabetes. They produce a magazine specifically for children and young people.

My Diabetes My Way

www.mydiabetesmyway.scot.nhs.uk

NHSScotland interactive diabetes website to help support people who have diabetes and their family and friends. You'll find leaflets, videos, educational tools and games containing information about diabetes.

13 Implementing the guideline

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

Implementation of national clinical guidelines is the responsibility of each NHS Board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

13.1 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

A cost and resource impact report and an associated spreadsheet have been developed to provide each NHS board with resource and cost information to support the implementation of the recommendations judged to have a material impact on resources (see Table 7). These documents are available from the SIGN website: www.sign.ac.uk

Table 7: Recommendations costed in the cost and resource impact report

Recommendation	Section
A Obese adults with type 2 diabetes should be offered individualised interventions to encourage weight loss (including lifestyle, pharmacological or surgical interventions) in order to improve metabolic control.	3.6.2
A Children and adults with type 1 and type 2 diabetes should be offered psychological interventions (including motivational interviewing, goal setting skills and CBT) to improve glycaemic control in the short and medium term.	4.3.3
A CSII therapy is associated with modest improvements in glycaemic control and should be considered for patients unable to achieve their glycaemic targets.	5.3.2
B CSII therapy should be considered in patients who experience recurring episodes of severe hypoglycaemia.	5.3.2
<input checked="" type="checkbox"/> An insulin pump is recommended for those with very low basal insulin requirements (such as infants and very young children), for whom even small doses of basal insulin analogue may result in hypoglycaemia.	5.3.2
<input checked="" type="checkbox"/> Pump therapy should be available from a local multidisciplinary pump clinic for patients who have undertaken structured education.	5.3.2
A Soluble human insulin or rapid-acting insulin analogues can be used when intensifying insulin regimens to improve or maintain glycaemic control.	6.10.5
A A suitable programme to detect and treat gestational diabetes should be offered to all women in pregnancy.	7.8
A Intensive lipid-lowering therapy with atorvastatin 80 mg should be considered for patients with diabetes and acute coronary syndromes, objective evidence of coronary heart disease on angiography or following coronary revascularisation procedures.	8.4.7
A In patients with diabetes, DES are recommended as opposed to BMS in stable coronary heart disease or non-ST elevation myocardial infarction to reduce in-stent re-stenosis and target lesion revascularisation.	8.6.4

13.2 AUDITING CURRENT PRACTICE

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

The guideline development group has identified the following as key points to audit to assist with the implementation of this guideline:

13.2.1 LIFESTYLE MANAGEMENT

- The availability of specific structured education programmes for people with type 1 or type 2 diabetes at Health Board level and capacity of available programmes.
- The proportion of patients with type 1 and type 2 diabetes being offered structured education, including measurement of the proportion who are invited, and who fail to attend.
- Evaluation of glycaemic and QoL outcomes in patients attending structured education programmes.
- Availability of services in each Health Board for patients with diabetes who are obese/overweight including, dietetic, psychological support and bariatric surgery.
- Measurement of outcomes (weight, diabetes resolution, glycaemia) in patients receiving these interventions.

13.2.2 PSYCHOSOCIAL FACTORS

- Extent to which services regularly assess psychological problems in children and adults.
- Frequency with which the service refers children and adults for psychological interventions to improve glycaemic control.

13.2.3 MANAGEMENT OF TYPE 1 DIABETES

- Monitoring of provision of a private area for SMBG and insulin injection at school, and the availability of assistance for these activities.
- Examples of good working collaboration between education and health services should be recorded.

13.2.4 PHARMACOLOGICAL MANAGEMENT OF GLYCAEMIC CONTROL IN PEOPLE WITH TYPE 2 DIABETES

- Rates of use of NPH insulin versus long-acting analogue insulin as initial basal insulin.
- Rates of continuation of metformin and sulphonylureas in people with type 2 diabetes when basal insulin is commenced.
- Rates of discontinuation of sulphonylureas in people with type 2 diabetes when prandial insulin is added to basal insulin.
- Rates of pancreatitis and other GI symptoms in people prescribed GLP-1 agonists.
- Rates of infections in people prescribed DPP-4 inhibitors.

13.2.5 MANAGEMENT OF DIABETES IN PREGNANCY

- Outcomes of managing women with type 1 and type 2 diabetes during pregnancy including birth weight, rate of macrosomia, intrauterine growth retardation and shoulder dystocia, caesarean section rate, perinatal mortality rate and neonatal hypoglycaemia.
- Number of women diagnosed with GDM under the international consensus criteria.
- Outcomes of managing women with GDM using the international consensus criteria including birth weight, rate of macrosomia, intrauterine growth retardation and shoulder dystocia, caesarean section rate, perinatal mortality rate and neonatal hypoglycaemia.

13.2.6 MANAGEMENT OF DIABETIC CARDIOVASCULAR DISEASE

- Numbers of diabetic patients aged over 40 years on statins.
- Numbers of patients receiving intensive glycaemic control following acute coronary syndromes.
- Numbers of patients with previous acute coronary syndromes on beta blockers.
- Numbers of patients with chronic heart failure on beta blockers.

13.2.7 MANAGEMENT OF KIDNEY DISEASE IN DIABETES

- Proportion of people with diabetes who have eGFR and urine protein excretion assessed annually.
- Proportion of people with diabetes who have stage 3, 4 and 5 CKD and who have microalbuminuria and diabetic nephropathy.
- Proportion of people with diabetic kidney disease who are receiving an ACE inhibitor or an ARB.
- Proportion of people with diabetic kidney disease who have BP > 120/70 and 135/75 mm Hg respectively.
- Proportion of people with diabetes and CKD stage 3-5 who have haemoglobin checked annually.

13.2.8 PREVENTION OF VISUAL IMPAIRMENT

- The proportion of patients receiving retinal screening within the appropriate timescale for them (ie 6, 12 or 24 months).
- The proportion of patients with referable retinopathy.
- The mean, and maximum time from the episode of retinal screening to being seen in an ophthalmology clinic.
- The mean, and maximum time from retinal screening to receiving laser photocoagulation, where required.
- Retinal grading should undergo internal and external quality assurance.
- The proportion of patients registered with partial vision or blindness who receive disability benefits.
- The proportion of patients registered with partial vision or blindness who receive low vision aids.
- The proportion of eligible patients receiving the national Diabetes Retinal Screening leaflet.

13.2.9 MANAGEMENT OF DIABETIC FOOT DISEASE

- To determine if the traffic light system improves care.
- Implementation of patient leaflets and patient satisfaction with them.

13.3 ADDITIONAL ADVICE TO NHSSCOTLAND FROM NHS QUALITY IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

The Scottish Medicines Consortium has published guidance on a range of drugs used in the management of people with diabetes. A summary of these findings is available from the SIGN web site (www.sign.ac.uk).

NHS Quality Improvement Scotland advises that the recommendations in the following NICE technology appraisals are as valid for Scotland as for England and Wales:

- NICE Technology Appraisal Guidance No 53 - The use of long-acting insulin analogues for the treatment of diabetes - insulin glargine (Dec 2002)
- NICE Technology Appraisal Guidance 60 - guidance on the use of patient-education models for diabetes (May 2003)
- NICE (Multiple) Technology Appraisal Guidance No 151 - insulin pump therapy (Jul 2008).

14 The evidence base

14.1 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 a SIGN Information Officer. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2003-2009. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence.

14.1.1 LITERATURE SEARCH FOR PATIENT ISSUES

At the start of the guideline development process, a SIGN Information Officer conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to management of patients with diabetes. Databases searched include Medline, Embase, Cinahl and PsycINFO, and the results were summarised and presented to the guideline development group. A copy of the Medline version of the patient search strategy is available on the SIGN website.

14.2 RECOMMENDATIONS FOR RESEARCH

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline (*see Annex 1*). The following areas for further research have been identified:

14.2.1 LIFESTYLE MANAGEMENT

- Further research on the role of blood glucose monitoring and its cost effectiveness in specific subgroups of patients with type 2 diabetes.
- Head-to-head comparisons of interventions to reduce obesity in patients with type 2 diabetes, including effect on glycaemic control.
- Further research on the benefits of blood ketone monitoring.
- Which smoking cessation interventions are most effective in people with diabetes?

14.2.2 PSYCHOSOCIAL FACTORS

- Longitudinal studies of newly diagnosed patients, investigating causal links between diabetes, symptoms, self management and aspects of psychological functioning are required.
- Clinically relevant screening tools to identify psychological problems require validation for use with adults and/or children with diabetes.
- Most research has focused on HbA1c as the main outcome for self management interventions in diabetes. There is a need for theoretically based research studies which identify the relationship between specific self-management behaviours and positive psychological outcomes (such as quality of life, well-being) in diabetes.
- Effective treatments for clinically significant psychological problems in adults and children with diabetes.
- Effectiveness of psychological interventions to improve shorter and longer term health outcomes for specific groups such as those with poor control.

14.2.3 MANAGEMENT OF TYPE 1 DIABETES

- Evidence for an optimal range of HbA1c targets for adults and children with type 1 diabetes based on intensive treat to target trials.
- Large RCTs comparing CSII therapy to MDI therapy with insulin analogues, which assess glycaemic control and rates of hypoglycaemia, DKA and validated QoL assessment are lacking. Such studies should not restrict entry on the basis of hypoglycaemia.
- Does managing hospitalised patients with type 1 diabetes with a dedicated inpatient diabetes team lead to shorter stays in hospital, reduced morbidity and reduced costs compared with standard care?
- Identification of the optimal evidence based process for transition from paediatric to adult services, taking into account measures of glycaemic control, psychological adjustment, loss to follow up and provision of specialist resources.

14.2.4 PHARMACOLOGICAL MANAGEMENT OF GLYCAEMIC CONTROL IN PEOPLE WITH TYPE 2 DIABETES

- What causes adverse outcomes in people with type 2 diabetes with long duration of disease when using an HbA1c target of 6.0%, and how can such harm be avoided?
- Which oral glucose-lowering agent (sulphonylurea, thiazolidinedione, DPP-4 inhibitor) should be added in 'second line' after metformin to achieve best cardiovascular and microvascular outcomes while avoiding hypoglycaemia?
- In adults with type 1 diabetes mellitus does metformin therapy added to usual insulin and standard treatment prevent major cardiovascular disease?
- Can novel genetic, proteomic, metabolomic or other 'biomarkers' guide prescribing of oral glucose-lowering agents in type 2 diabetes, ie predict individual patient HbA1c responses?

14.2.5 MANAGEMENT OF DIABETES IN PREGNANCY

- Optimal timing of delivery in pregnant women with diabetes.
- Frequency and modality of retinopathy screening in pregnant women.

14.2.6 MANAGEMENT OF DIABETIC CARDIOVASCULAR DISEASE

- Intensive management of hyperglycaemia following acute coronary syndromes.
- Drug treatment of chronic heart failure in patients with diabetes.
- Glycaemic treatment of diabetic patients with chronic heart failure.
- Possible benefits of non-statin lipid-lowering drugs in patients with diabetes.

14.2.7 MANAGEMENT OF KIDNEY DISEASE IN DIABETES

- What are the mechanisms behind the racial differences in kidney disease prevalence and adverse outcomes?
- Do any anti-diabetic therapies have a specific reno-protective effect?
- In light of recent trial evidence, does blockade of the RAAS prevent the development of microalbuminuria in low-risk patients.
- Does combination therapy with both ACE inhibitors and ARBs have an additive effect in preventing the progression of diabetic kidney disease in high-risk patients and what is the prevalence of adverse events associated with such dual therapy?
- Do mineralocorticoid receptor antagonists and direct renin inhibitors prevent the progression of diabetic kidney disease?
- Does statin therapy prevent the progression of diabetic kidney disease?
- Do erythropoiesis-stimulating agents specifically improve outcomes in people with diabetes and kidney disease and what is the appropriate target haemoglobin concentration?

14.2.8 PREVENTION OF VISUAL IMPAIRMENT

- To ascertain whether or not there has been any marked change in the number of young people pre- and post-puberty with retinopathy, particularly in Scotland, bearing in mind the increased numbers diagnosed at earlier ages.
- The accuracy of automated grading measured against a gold-standard reference in cohorts of patients with different levels of retinal disease.
- The accuracy of OCT in screening for macular oedema.
- Identification of reasons for non-attendance at retinal screening and comparison of interventions to improve uptake.
- Investigation of non-use of low vision aids services in people who are eligible for these.

14.2.9 MANAGEMENT OF DIABETIC FOOT DISEASE

- Clinical and cost effectiveness of screening for diabetic foot disease.
- Effectiveness of different debridement techniques for improving healing outcomes in patients with active foot ulceration.
- Effectiveness of hyperbaric oxygen in improving ulcer healing outcomes in patients with active foot ulceration.
- Foot orthosis (construction, matching biomechanics with tissue mechanics).
- Role of vascular interventions in healed ulcers.
- Head-to-head comparisons of pharmacological and non-pharmacological interventions to treat painful diabetic neuropathy.
- Role of structured education in high-risk patients to affect ulcer events/amputation or preventing recurrent events in patients with leg ulcer.

14.3 REVIEW AND UPDATING

This guideline was issued in 2010 and will be considered for review in three years. Any updates to the guideline in the interim period will be noted on the SIGN website: www.sign.ac.uk

15 Development of the guideline

15.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of NHS Quality Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising clinicians 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

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15.2.5 CARDIOVASCULAR DISEASE SUBGROUP

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15.2.6 KIDNEY SUBGROUP

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15.2.7 VISUAL IMPAIRMENT SUBGROUP

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Dr John Hinnie	<i>Consultant in Endocrinology, Victoria Infirmary, Glasgow</i>
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15.2.8 FOOT DISEASE SUBGROUP

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The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest and further details of these are available on request from the SIGN Executive.

Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive.

15.2.9 PATIENT INVOLVEMENT

In addition to the identification of relevant patient issues from a broad literature search, SIGN involves patients and carers throughout the guideline development process in several ways. SIGN recruits a minimum of two patient representatives to guideline development groups by inviting nominations from the relevant 'umbrella', national and/or local patient-focused organisations in Scotland. Where organisations are unable to nominate, patient representatives are sought via other means, eg from consultation with health board public involvement staff. Further patient and public participation in guideline development was achieved by involving patients, carers and voluntary organisation representatives in the peer review stage of the guideline and specific guidance for lay reviewers was circulated. Members of the SIGN patient network were also invited to comment on the draft guideline section on provision of information.

15.2.10 ACKNOWLEDGEMENTS

SIGN would like to acknowledge the guideline development group responsible for the development of SIGN 55: Management of Diabetes, on which this guideline is based.

15.3 THE GUIDELINE STEERING GROUP

A steering group was established to oversee the work of the eight guideline development subgroups. It retained a strategic responsibility for activities concerning development, consultation and dissemination of the guideline recommendations. The steering group is composed of the chairs of each of the subgroups, and representatives from associated key organisations. It met regularly during the lifetime of the guideline.

Dr John McKnight (Chair)	<i>Consultant Physician, Diabetes Unit, Western General Hospital, Edinburgh</i>
Mr Naseem Anwar	<i>Director of Equality and Diversity, The University of Glasgow</i>
Dr Miles Fisher	<i>Chair of Cardiovascular Disease subgroup and Consultant Physician, Glasgow Royal Infirmary</i>
Dr Stephen Gallacher	<i>Chair of Lifestyle subgroup and Consultant Physician, Southern General Hospital, Glasgow</i>
Dr Roberta James	<i>Programme Manager, SIGN</i>
Mrs Jane-Claire Judson	<i>Director, Diabetes UK Scotland, Glasgow</i>
Dr Brian Kennon	<i>Chair of Foot Disease subgroup and Consultant Physician, Southern General Hospital, Glasgow</i>
Dr Graham Leese	<i>Chair of Visual Impairment subgroup and Consultant Physician, Ninewells Hospital and Medical School, Dundee</i>
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Mr David Paul	<i>Patient representative, Glasgow</i>
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All members of the steering group made declarations of interest and further details of these are available on request from the SIGN Executive.

15.4 CONSULTATION AND PEER REVIEW

15.4.1 PUBLIC CONSULTATION

The draft guideline was available on the SIGN website for a month to allow all interested parties to comment. Individuals and organisations which participated in the consultation are listed on the SIGN website (www.sign.ac.uk).

15.4.2 SPECIALIST REVIEW

This guideline was also reviewed in draft form by the following independent expert referees, who were invited to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments.

SIGN is very grateful to all of these experts for their contribution to the guideline.

Professor Cliff Bailey	<i>Professor of Clinical Science, School of Life and Health Sciences, Aston University, Birmingham</i>
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15.4.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows:

Dr Keith Brown	<i>Chair of SIGN; Co-Editor</i>
Ms Beatrice Cant	<i>SIGN Programme Manager</i>
Dr Sara Twaddle	<i>Director of SIGN; Co-Editor</i>

Abbreviations

4S	Scandinavian Simvastatin Study
AC	abdominal circumference
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	angiotensin converting enzyme
ACR	albumin/creatinine ratio
ACT	acceptance and commitment therapy
ADOPT	A Diabetes Outcome Progression
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation
AER	albumin excretion rate
AFCAPS/TexCAPS	Air Force/Texas Coronary Atherosclerosis Prevention Study
AIRE	Acute Infarction Ramipril Efficacy
ALLHAT	Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial
AR	absolute risk
ARB	angiotensin-II receptor blocker
ARI	absolute risk increase
ARR	absolute risk reduction
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
ASSIGN	assessing cardiovascular risk using SIGN guidelines to assign preventative treatment
BARI	Bypass Angioplasty Revascularization Investigation
BDI	Beck Depression Inventory
BGAT	Blood Glucose Awareness Training
BMI	body mass index
BMS	bare metal stents
BNF	British National Formulary
BP	blood pressure
BSA	body surface area
CABG	coronary artery bypass grafting
CAPRICORN	Carvedilol Post-Infarct Survival Control in Left Ventricular dysfunction
CARDS	Collaborative Atorvastatin Diabetes Study
CARE	Cholesterol and Recurrent Events
CBT	cognitive behavioural therapy
CCB	calcium channel blocker
CES-D	Centre for Epidemiological Studies–Depression Scale

CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CIBIS II	Cardiac Insufficiency Bisoprolol Study II
CKD	chronic kidney disease
CMG	continuous monitoring of interstitial glucose
COC	combined oral contraceptive
COMET	Carvedilol Or Metoprolol European Trial
COMMIT/CCS-2	Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study
CONSENSUS	Co-operative North Scandinavian Enalapril Survival Study
COPD	chronic obstructive pulmonary disease
COPERNICUS	Carvedilol Prospective Randomized Cumulative Survival Trial
CSII	continuous subcutaneous insulin infusion
CSMO	clinically significant macular oedema
CTG	cardiotocography
CURE	Clopidogrel in Unstable angina to prevent Recurrent ischemic Events
CVD	cardiovascular disease
DAFNE	Dose Adjustment for Normal Eating
DCCT	Diabetes Control and Complications Trial
DES	drug-eluting stents
DESMOND	Diabetes Education and Self-Management for Ongoing and Newly Diagnosed
DIGAMI	Diabetes mellitus, Insulin-Glucose infusion in Acute Myocardial Infarction
DKA	diabetic ketoacidosis
DPN	diabetic peripheral neuropathy
DPP-4	dipeptidyl peptidase-4
DR	diabetic retinopathy
DVLA	Driver and Vehicle Licensing Agency
EAST	Emory Angioplasty vs Surgery Trial
ES	effect size
ESRD	end-stage renal disease
ETDRS	Early Treatment Diabetic Retinopathy Study
EUROPA	European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
FPG	fasting plasma glucose

g-csf	granulocyte-colony stimulating factor
GDM	gestational diabetes mellitus
GFR	glomerular filtration rate
GHbSD	standard deviations of glycosylated haemoglobin
GI	glycaemic index
GLP-1	glucagon-like peptide 1
GP	general practitioner
GSD	guided self-determination
HAATT	Hypoglycemia Anticipation, Awareness and Treatment Training
HADS	Hospital Anxiety and Depression Scale
HAPO	Hyperglycaemia and Adverse Pregnancy Outcome
HbA1c	glycated haemoglobin
HDL	high density lipoprotein
HF	heart failure
HOPE	Heart Outcomes Prevention Evaluation
HOT	Hypertension Optimal Treatment
HPS	Heart Protection Study
HR	hazard ratio
HTA	Health Technology Assessment
IDNT	Irbesartan in Diabetic Nephropathy Trial
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
IUD	intrauterine device
IUGR	intrauterine growth restriction
IUS	intrauterine systems
JBS 2	Joint British Societies' guideline
KCND	Keeping Childbirth Natural and Dynamic
K/DOQI	Kidney Disease Outcomes Quality Initiative
LCD	low calorie diet
LDL	low density lipoprotein
LED	low energy diets
LoS	length of stay
LVSD	left ventricular systolic dysfunction
MDI	multiple daily injections
MDRD	Modification of Diet in Renal Disease
MERIT-HF	MEtoprolol CR/XL Randomised Intervention Trial in congestive Heart Failure

MI	myocardial infarction
MotI	motivational interviewing
MR	modified release
MRB	mineralocorticoid receptor blocker
MRI	magnetic resonance imaging
MTA	multiple technology appraisal
NHS QIS	NHS Quality Improvement Scotland
NICE	National Institute for Health and Clinical Excellence
NPH	neutral protamine hagedorm
NPWT	negative pressure wound therapy
NYHA	New York Heart Association classification
OCT	optical coherence tomography
OFC	occipito-frontal head circumference
OGTT	oral glucose tolerance test
OR	odds ratio
PAD	peripheral arterial disease
PAID	Problem Areas in Diabetes
PCI	percutaneous coronary intervention
PCR	protein/creatinine ratio
PCT	primary care trust
PEACE	Prevention of Events with Angiotensin Converting Enzyme Inhibition
PES	paclitaxel-eluting stents
PHQ-9	Patient Health Questionnaire
PKC-DRS	Protein Kinase C Diabetic Retinopathy Study
PROACTIVE	PROspective pioglitAzone Clinical Trial In macroVascular Events
PROVE-IT	Pravastatin or Atorvastatin Evaluation and Infection Therapy
PSMF	protein sparing modified fast
PTCA	percutaneous transluminal coronary angioplasty
PUFA	polyunsaturated fatty acid
QALY	quality adjusted life year
QOF	quality outcomes framework
QoL	quality of life
QUIET	QUinapril Ischemic Event Trial
RAAS	renin-angiotensin-aldosterone system
RCT	randomised controlled trial
RECORD	Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes
RENAAL	Reduction of Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan

REPOSE	Relative Effectiveness of Pumps Over MDI and Structured Education
RR	relative risk
RRT	renal replacement therapy
SBP	systolic blood pressure
SCID	Structured Clinical Interview for DSM-IV-TR
SD	standard deviation
SE	standard error
SENIORS	Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors
SES	sirolimus-eluting stents
SGA	small for gestational age
SIGN	Scottish Intercollegiate Guidelines Network
SMBG	self monitoring of blood glucose
SMC	Scottish Medicines Consortium
SMD	standardised mean difference
SMUG	self monitoring of urine glucose
SOLVD	Studies of Left Ventricular Dysfunction
SSRI	selective serotonin reuptake inhibitor
SU	sulphonylurea
TCA	tricyclic antidepressant
TG	triglycerides
TNT	Treating to New Targets
TZD	thiazolidinedione
UK	United Kingdom
UKPDS	United Kingdom Prospective Diabetes Study
USA	United States of America
VADT	Veterans Affairs Diabetes Trial
VA-HIT	Veterans Affairs High-Density Lipoprotein Intervention Trial
VEGF	vascular endothelial growth factor
VLED	very low energy diet
WHO	World Health Organization
WMD	weighted mean difference

Annex 1

Key questions addressed in this update

LIFESTYLE SUBGROUP	
Key question	See guideline section
1. What is the evidence that weight loss (5-10%) in patients with type 2 diabetes has a beneficial effect on glycaemia, morbidity (retinopathy, renal, MI and stroke), depression and quality of life? (Consider long term and short term weight loss)	3.6
2. In type 2 diabetes patients over 18 with a BMI over 30, what is the clinical and cost effectiveness of bariatric surgery in terms of quality of life, morbidity (glycaemia and diabetes associated complications) and mortality?	3.6.2
3. In patients with diabetes what are the outcomes of group education, individualised (one on one) education and structured education (such as DAFNE, BERTIE, RECLAIM for type 1; DESMOND for type 2), compared in terms of patient satisfaction, QoL, psychological well-being (depression, confidence, reduced stress), cost effectiveness, glycaemic control (HbA1c, hypo consider major and minor and hyperglycaemia), weight loss (where applicable) and hospital admissions? – include children and adults, type 1 and type 2 diabetes	3.2
4. What evidence is there to support (i) self monitoring of blood glucose (ii) continuous glucose monitoring as a strategy to improve glycaemic control (HbA1c, rates of hypo and hyperglycaemia), micro/macrovacular diseases and patient satisfaction in a) type 1 diabetes b) type 2 diabetes? (Also consider during periods of fasting, during pregnancy, around the time of exercise, or during periods of illness)	3.3.1, 3.3.2
5. (a) In patients with type 1 diabetes, does ketone monitoring reduce rates of hospital admission, rates of DKA, mortality, or improve glycaemic control (HbA1c, rates of hypo/hyperglycaemia)? (b) Is there evidence that blood is better (more sensitive/specific than urine (or vice versa) for monitoring ketones?	3.3.4 3.3.4
6. In patients with type 2 diabetes does self monitoring of urinary glucose reduce rates of hospital admission, rates of DKA, mortality, and improve glycaemic control (HbA1C, rates of hypo/hyperglycaemia)?	3.3.4
7. Is there a validated screening tool for use in primary and secondary care to detect (a) depression (b) anxiety (c) eating disorders in patients with type 1 and type 2 diabetes?	4.2
8. What is the evidence that psychological interventions (motivational interviewing, goal setting, coping skills and CBT) are effective in supporting treatment adherence, lifestyle change and self-management in patients with type 1 and type 2 diabetes?	4.3

<p>9. Are structured exercise programmes or exercise referral programmes (such as exercise on prescription) cost effective and beneficial in terms of:</p> <ul style="list-style-type: none"> ▪ weight loss ▪ improvements in glycaemic control (hypo/hyperglycaemia HbA1C) ▪ reduction in macrovascular and microvascular complications ▪ reductions in mortality ▪ psychological outcomes in patients with type 1 OR type 2 diabetes? <p>Consider audit data, uptake, adherence and adverse effects (eg hypoglycaemia)</p>	3.5.4-3.5.7
<p>10. Does physical activity (and how much/what kind) a) improve glycaemic control (hypo/ hyperglycaemia/ HbA1c) b) reduce macrovascular and microvascular complications or c) reduce mortality in patients with type 1 OR type 2 diabetes?</p> <p>Include studies with minimum three months follow up</p>	3.5
<p>11. In patients with type 1 and type 2 diabetes, are any specific dietary interventions effective in terms of patient satisfaction, quality of life, glycaemic control (HbA1c, hypo major and minor and hyperglycaemia), weight loss, reduced hospital admissions, improved haemoglobin A1C, reduced blood pressure, and improved lipid pattern?</p> <p>Consider:</p> <ul style="list-style-type: none"> ▪ low carbohydrate/restricted carbohydrate ▪ low GI ▪ healthy eating advice ▪ atkins/ketogenic. 	3.7
<p>12. Is there any evidence that particular levels of alcohol consumption result in additional harm to diabetic populations as compared to non-diabetic populations in terms of cardiovascular risk and mortality?</p>	3.8
<p>13. Do patients with diabetes benefit from different smoking cessation interventions compared with the non-diabetic population?</p>	3.4.2

TYPE 1 DIABETES SUBGROUP

Key question	See guideline section
1. In people with type 1 diabetes, which of the following therapies are most beneficial in terms of glycaemic control, hypoglycaemia, diabetic ketoacidosis and quality of life (of patient/parents/carers)? <ul style="list-style-type: none"> ▪ multiple injection therapy (≥ 3 injections per day) ▪ insulin pump therapy. 	5.3.2
2. Which of the following insulin in people with type 1 diabetes is most beneficial in terms of glycaemic control (HbA1c), hypoglycaemia and quality of life? <ul style="list-style-type: none"> ▪ analogue (glargine; detemir; aspart; lispro; glulisine) ▪ non-analogue. 	5.3.2
3. In adolescents with type 1 diabetes, what is the best model of transition care from paediatric to adult services in terms of glycaemic control, patient satisfaction, quality of life, non-attendance rates and hospital admissions?	5.3.7
4. What is the evidence that children under 18 yrs (nursery; school; college) offered management support with their type 1 diabetes at (nursery; school; college) have fewer hypos, better glycaemic control and improved quality of life in comparison to those not offered such support?	5.3.8
5. In people with type 1 diabetes, is management with an integrated care pathway (ICP) versus no ICP associated with improved outcome in terms of hypoglycaemia, mortality, duration of inpatient stay and morbidity (complications of treatment, infection, hypokalaemia, cerebral oedema)?	5.3.5
6. What is the evidence that specialist out of hours diabetes helplines prevent unnecessary hospital admissions; prevent acute metabolic upset (DKA); and increase user satisfaction?	5.3.6
7. In adults with type 1 diabetes in the hospital setting, what is the evidence that an inpatient diabetes specialist team (nurse/educator) compared to no specialist team shortens length of stay and reduces complications [infections, hypoglycaemia, hyperglycaemia]?	5.3.4
8. In people with type 1 diabetes in the hospital setting, what is the evidence that self care/or carer care/or a specialist team/nurse (insulin administration, glucose monitoring and diet) compared to routine ward care (non-diabetes specialists) shorten length of stay, improve patient satisfaction and reduce complications (infections, hypoglycaemia, hyperglycaemia)?	5.3.4
9. What are the influences of psychological or social factors on diabetic outcomes in people with diabetes?	4.1
10. Are there any interventions which affect the specific psychological or social factors noted in question 9 which also affect improvement in diabetes outcomes?	4.2

TYPE 2 DIABETES SUBGROUP	
Key question	See guideline section
1. In adult patients with type 2 diabetes, what is the evidence that reducing HbA1c to specified targets (below 7.5%) affects mortality, cardiovascular morbidity and mortality, microvascular morbidity, weight, hypoglycaemia and other adverse events?	6.2
2. In adults with type 2 diabetes (newly diagnosed v established disease or younger v older?) what is the evidence that the following therapies influence mortality, cardiovascular morbidity, microvascular morbidity, HbA1c, lipids, blood pressure, weight, hypoglycaemia, other adverse events and quality of life?: <ul style="list-style-type: none"> ▪ metformin (<i>glucophage</i>) ▪ sulphonylureas (chlorpropamide, glibenclamide, gliclazide, glimepiride, glipizide, tolbutamide) ▪ metiglinides (repaglinide, nateglinide). 	6.3 6.4 6.8
3. In adults with type 2 diabetes what is the evidence that the following therapies (compared to placebo and each other) affect mortality, cardiovascular morbidity and mortality, microvascular morbidity, HbA1c (follow up of longer than 6 months), weight, hypoglycaemia and other adverse events? <ul style="list-style-type: none"> ▪ DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin) ▪ GLP-1 analogues (exenatide, liraglutide). 	6.6 6.9
4. In adults with type 2 diabetes what is the evidence that the following therapies (compared to placebo and each other) affect mortality, cardiovascular morbidity and mortality, microvascular morbidity, HbA1c (follow up of longer than 6 months), weight, hypoglycaemia and other adverse events?: <ul style="list-style-type: none"> ▪ insulin. 	6.10
5. In adults with type 2 diabetes what is the evidence that the following therapies (compared to placebo and each other) affect mortality, cardiovascular morbidity and mortality, microvascular morbidity, HbA1c (follow up of longer than 6 months), weight, hypoglycaemia and other adverse events?: <ul style="list-style-type: none"> ▪ alpha-glucosidase inhibitors (acarbose, Glucobay) ▪ thiazolidinediones (pioglitazone, rosiglitazone). 	6.7 6.5

PREGNANCY SUBGROUP	
Key question	See guideline section
1. What is the optimal pre-pregnancy HbA1c and risk of problems (congenital anomalies, miscarriage and hypoglycaemia) depending on HbA1c?	7.3.1
2. In pre-pregnant women do structured education programmes improve pregnancy outcomes (congenital anomalies, miscarriage, intrauterine death, macrosomia, preterm labour, pre-eclampsia, neonatal unit admission, hypoglycaemia) compared to standard diabetes care?	7.3
3. What are the optimum targets for blood glucose during pregnancy (type 1 or type 2 diabetes or gestational diabetes) to improve outcome (miscarriage, intrauterine death, macrosomia, pre-term labour, pre-eclampsia, neonatal unit admission, hypoglycaemia, mode of delivery)?	7.5.1
4. Do analogue insulins or insulin pump therapy compared to standard insulin regimens improve pregnancy outcomes (congenital anomalies, miscarriage, intrauterine death, macrosomia, pre-term labour, pre-eclampsia, neonatal unit admission or frequency of hypoglycaemia, mode of delivery) in type 1 or type 2 diabetes or gestational diabetes? Consider: subcutaneous insulin infusion, continuous basal delivery, lantus, detanir, levenir, novoropid, aspart, hunalog, lispro	7.5.2
5. Which oral hypoglycaemics are safe and effective in pregnancy (outcomes: congenital anomalies, miscarriage, intrauterine death, macrosomia, pre-term labour, pre-eclampsia, neonatal unit admission or frequency of hypoglycaemia, mode of delivery) (metformin, glibenclamide, glyburide and oral hypoglycaemics)?	7.3.2, 7.8.3
6. Compared to standard antenatal care pathway, by what methods and when should fetal growth and well-being be monitored to improve pregnancy outcomes in type 1, type 2 and GDM, including macrosomia, intrauterine growth retardation, shoulder dystocia, perinatal mortality, perinatal morbidity and mode of delivery? Consider: fetal growth/ cardiotocograph/ biophysical profile/ umbilical artery Doppler	7.7, 7.8
7. When and by what method should women be offered screening for congenital malformations and counselling?	7.7
8. Does screening for, and diagnosis of, gestational diabetes alter pregnancy outcomes (including macrosomia, perinatal mortality, perinatal morbidity and mode of delivery)? Consider who should be screened: obese, previous delivery > 4 kg baby, family history diabetes, polycystic ovarian syndrome, previous GDM	7.8.1
9. Is there a threshold in fasting, one hour or two hour glucose values above which adverse pregnancy outcomes (including macrosomia, perinatal mortality, perinatal morbidity and mode of delivery) are increased?	7.8.1, 7.8.2
10. Does lowering of blood glucose during pregnancy in women with gestational diabetes alter pregnancy outcomes (including macrosomia, perinatal mortality, perinatal morbidity and mode of delivery)?	7.8.3
11. What is the risk of type 2 diabetes after GDM?	7.12
12. Which interventions decrease the incidence of type 2 diabetes after GDM including information and follow up?	7.12

CARDIOVASCULAR DISEASE SUBGROUP	
Key question	See guideline section
1. In people with type 2 diabetes with or without cardiovascular disease, does treatment with glitazone/thiazolidine/TZD compared to the following improve cardiovascular outcomes (define), reduce mortality and incidence of MI and stroke? <ul style="list-style-type: none"> ▪ placebo ▪ metformin ▪ sulphonyl urea ▪ insulin. 	6.3.4, 6.4.3, 6.5.2, 6.5.5
2. In people with type 2 diabetes with or without cardiovascular disease, what is the optimum target for glycaemic control/HbA1c to reduce cardiovascular disease (all-cause death, MI, stroke, CV death)?	6.2
3. Which patients with diabetes without CV disease (with or without renal disease) should have a statin to reduce cardiovascular outcomes (death, MI, CVA, stroke)?	8.3.2
4. What is the optimum statin and statin dose to reduce cardiovascular events (death, MI, CVA, stroke) in people with diabetes? Should treatment be based on treat-to-target? <p>Consider:</p> <ul style="list-style-type: none"> ▪ atorvastatin ▪ simvastatin ▪ pravastatin ▪ rosuvastatin. 	8.3.2, 8.4.7, 8.6.2
5. In patients with diabetes do angiotensin receptor blockers (ARBs) (alone or in combination with ACE inhibitor) reduce risk of cardiovascular events (death, MI, CV death, stroke, PAD) (not post-MI and not heart failure as covered by SIGN 93 and 95) but with stable CHD or CV risk?	8.3.2
6. What is the systolic blood pressure target for patients with diabetes (adults, children, type 1, type 2, ethnicity) with or without complications in terms of cardiovascular outcomes (death, MI, CVA, stroke)?	8.3.2
7. Which class of blood pressure lowering drug is better for cardiovascular protection in all patients with diabetes and raised blood pressure in terms of cardiovascular outcomes (death, MI, CV death, stroke, PAD)? <ul style="list-style-type: none"> ▪ ACE inhibitor ▪ Ca channel blocker ▪ ARB ▪ diuretic (inc. indapamide) ▪ beta blockers ▪ alpha blockers. 	8.3.2
8. In people with diabetes without cardiovascular disease, does aspirin/ clopidogrel (compared to placebo) reduce the risk of (death, MI, CV death, stroke, PAD)? <p>Balance against risk of haemorrhage (GI and cerebral).</p>	8.3.2

<p>9. In patients with diabetes with or without cardiovascular disease, do the following lipid-lowering therapies (compared to placebo) improve cardiovascular outcomes (death, MI, CVA, stroke)?</p> <ul style="list-style-type: none"> ▪ gemfibrozil ▪ bezafibrate ▪ fenofibrate ▪ nicotinamide ▪ ezetimibe? 	8.3.2, 8.4.7
<p>10. In patients with diabetes and heart failure, do the following anti-hyperglycaemic therapies increase/decrease hospitalisations due to heart failure, death, MI, CV death, stroke?</p> <ul style="list-style-type: none"> ▪ metformin ▪ sulphonylurea ▪ glitazones ▪ insulin ▪ DPP4/IV (dipeptidyl peptidase inhibitors, gliptins) ▪ exenatide/incretin mimetics. 	8.5.1
<p>11. What is the optimal stent in people with diabetes undergoing PCI?</p> <ul style="list-style-type: none"> - drug-eluting (sirolimus; paclitaxel) - bare metal <p>Outcomes: mortality, MI, restenosis, rehospitalisation</p>	8.6.4

KIDNEY DISEASE SUBGROUP	
Key question	See guideline section
1. What is the prevalence of kidney disease in people with type 1 and type 2 diabetes and what is the rate of progression?	9.2
2. What is the aetiology of CKD (include microalbuminuria, proteinuria plus terms such as chronic renal insufficiency) in people with type 1 and type 2 diabetes?	9.2.1
3. Is there an indication for timed urine collections in the assessment of diabetic patients?	9.3.2
4. In patients with diabetes, what is the accuracy of near patient testing (compared to standard laboratory tests?) for the diagnosis of microalbuminuria?	9.3
5. In patients with diabetes what is the optimum screening interval for microalbuminuria?	9.3.2
6. In patients with diabetes and raised ACR how often and when should repeat estimates of ACR be performed?	9.3.2
7. In urinalysis of patients with diabetes, does the sample need to be first voided urine or can it be assessed at any time of day?	9.3.2
8. What is the incidence and prevalence of nephropathy in children < 18 years with diabetes?	9.2
9. In patients with diabetes and raised ACR when are additional investigations (eg ultrasonography of kidneys; auto-antibody testing, renal angiography, biopsy) indicated? (renal artery stenosis)	9.4
10. What is the prevalence of USS (ultrasound scan) abnormalities in people with diabetes and CKD?	9.4
11. What is the evidence that lowering blood pressure reduces the development and progression of CKD in diabetes? NB CKD includes microalbuminuria/proteinuria.	9.5.3
12. What is the evidence that reducing proteinuria reduces the development and progression of CKD in diabetes?	9.5.2
13. What is the evidence that ACEI, ARBs, spironolactone and direct renin inhibitors and/or combination therapy reduces the development and progression of CKD in diabetes?	9.5.4, 9.5.5
14. Do other classes of antihypertensive agents (eg beta blockers and calcium antagonists) reduce the development and progression of CKD in diabetes?	9.5.3
15. What is the incidence of hyperkalaemia and deteriorating renal function in people with diabetes treated with ACEI, ARBs, spironolactone and direct renin inhibitors and/or combination therapy?	9.5.4
16. Does race affect the efficacy of antihypertensive therapy in people with diabetes and CKD?	9.5.6
17. What is the prevalence of hyperkalaemia, anaemia, metabolic acidosis and secondary hyperparathyroidism in CKD in diabetes?	9.6.1-9.6.3

<p>18. Which of the following agents/factors influence risk of development or progression of diabetic nephropathy?</p> <ul style="list-style-type: none"> ▪ glycaemic control with: <ul style="list-style-type: none"> ◇ metformin ◇ sulphonylureas ◇ thiazolidinediones ◇ peptidase IV inhibitors ◇ exenatide ◇ insulin ▪ orlistat ▪ sibutramine ▪ rimonabant ▪ lipid-lowering therapy ▪ smoking ▪ exercise ▪ weight loss ▪ multifactorial intervention. 	9.5.1
<p>19. In people with diabetes < 40 years with diabetic nephropathy, does statin and aspirin therapy prevent the development of cardiovascular disease?</p>	9.5.7, 9.5.9
<p>20. Is there evidence that joint diabetes/nephrology clinics result in better outcomes?</p>	9.7
<p>21. Should people with diabetes on kidney dialysis continue to be followed in diabetes clinics?</p>	9.7

VISUAL IMPAIRMENT SUBGROUP	
Key question	See guideline section
1. Is there any evidence to indicate that in patients with diabetes the following risk factors affect the development and/or progression of diabetic retinopathy a) smoking b) cholesterol c) BP below 140/80 mm Hg?	10.1.1
2. Is there any evidence of diabetic macular oedema or diabetic ischaemic maculopathy or proliferative diabetic retinopathy under the age of 12 years?	10.2.1
3. Have the following factors been shown to increase, or decrease, the uptake of diabetic eye screening: a) routine use of mydriasis b) social deprivation c) rural living d) frequency of screening?	10.2.2
4. How frequently should patients with diabetes be screened for retinopathy to ensure prompt identification of referable retinopathy?	10.2.1
5. What is the sensitivity and specificity of the following for detecting diabetic macular oedema or proliferative diabetic retinopathy: a) one-field retinal photography b) two-field retinal photography c) automated grading d) WSLO (wide angle scanning laser ophthalmoscopy) e) OTC (optical coherence tomography)?	10.2.2, 10.2.3
6. What is the best surrogate retinal feature to predict macular oedema (or clinically significant macular oedema)? Consider: microaneurysm, blot haemorrhage, exudates, circinate	
7. What is the optimal laser treatment for: a) proliferative diabetic retinopathy and b) diabetic macular oedema?	10.3.1
8. What pharmacological agents reduce the development or progression of diabetic retinopathy, and are independent of blood pressure and glucose effects: a) statins b) fibrates (fenofibrate) c) ACE Inhibitors d) angiotensin receptor blockers (ARB) e) PKC Inhibitors f) VEGF aptamers g) intraocular steroids h) somatostatin analogues and pegvisomant?	10.3.4
9. Does cataract extraction affect the development or progression of diabetic retinopathy?	10.3.3
10. Is there any evidence of programmes which provide support and assistance to improve the quality of life and functional ability of people with diabetes and visual impairment?	10.4

FOOT DISEASE SUBGROUP	
Key question	See guideline section
<p>1. Does a structured screening programme versus no screening in patients with diabetes result in:</p> <ul style="list-style-type: none"> ▪ prevention of ulceration ▪ decreased incidence of major amputation? <p>Consider who conducts screening</p>	11.2.1
<p>2. In the following groups of people, what is the evidence that specialist/prescription/therapeutic bespoke footwear/insoles or orthosis lowers the risk of development of ulceration or amputation:</p> <ul style="list-style-type: none"> ▪ those with arterial disease ▪ those with previous ulceration ▪ those with diabetic neuropathy ▪ those with deformity? 	11.2.3
<p>3. In diabetic patients with active plantar foot ulceration is there any evidence that the following interventions improve ulcer healing rate, reduce incidence of amputation, and reduce incidence of new ulceration:</p> <ul style="list-style-type: none"> ▪ total contact casting (plaster bootie) ▪ air cast boot (remove and irremovable) (axial offloading, CROW walker) ▪ non-weight bearing ▪ additional orthosis eg forefoot offloading (IPOS; DARCO)? 	11.3.3
<p>4. In diabetic patients with active foot ulceration is there any evidence that vacuum-assisted wound closure devices/topical negative pressure devices improve healing outcomes?</p>	11.3.5
<p>5. In diabetic patients with active foot ulceration is there any evidence that the following debridement techniques improve healing outcomes:</p> <ul style="list-style-type: none"> ▪ surgical debridement ▪ larvae therapy ▪ local sharp debridement ▪ hydrojet therapy – ‘versajet’? 	11.3.2
<p>6. In diabetic patients with critical limb ischaemia (including ulceration, rest pain and tissue loss) is there any evidence that vascular intervention (angioplasty/bypass) improves healing outcomes or decreases major amputation rates, necrosis and gangrene?</p>	11.3.6
<p>7. What is the evidence that referral to a multidisciplinary diabetic foot team improves the outcomes of patients with active diabetes foot ulceration? (Outcomes: QoL, ulcer healing rate, ulcer re-occurrence rate, death, amputation)?</p>	11.3.1
<p>8. In patients with diabetes, what is the evidence to improve the management of Charcot neuropathy? [Outcomes: reduction in pain, ulceration rate, amputation rate, disease duration and deformity</p>	11.3.7

<p>9. What is the most effective agent for the treatment of painful diabetic neuropathy (outcomes: pain reduction, QoL):</p> <ul style="list-style-type: none">▪ gabapentin▪ pregabalin▪ duloxetine▪ opiates▪ tricyclic antidepressants▪ carbamazepine▪ tramadol?	11.4.1
<p>10. What is the most effective non-pharmacological treatment of painful diabetic neuropathy? [outcomes: pain reduction, QoL]:</p> <ul style="list-style-type: none">▪ acupuncture▪ cognitive behavioural therapy▪ anodyne therapy▪ TENS?	11.4.2

Annex 2

Conversion table for HbA1c formats

From June 2009 to June 2011 HbA1c will be dual reported in DCCT-aligned format (measured in percentage) and IFCC-aligned format (measured in mmol/mol). The conversion formulae for these formats are as follows:

DCCT-aligned HbA1c value = (0.0915 x IFCC-aligned value) + 2.15 %

IFCC-aligned HbA1c value = (10.93 x DCCT-aligned value) – 23.5 mmol/mol

DCCT-aligned HbA1c (%)	IFCC-aligned HbA1c (mmol/mol)	DCCT-aligned HbA1c (%)	IFCC-aligned HbA1c (mmol/mol)
4.0	20	8.0	64
4.1	21	8.1	65
4.2	22	8.2	66
4.3	23	8.3	67
4.4	25	8.4	68
4.5	26	8.5	69
4.6	27	8.6	70
4.7	28	8.7	72
4.8	29	8.8	73
4.9	30	8.9	74
5.0	31	9.0	75
5.1	32	9.1	76
5.2	33	9.2	77
5.3	34	9.3	78
5.4	36	9.4	79
5.5	37	9.5	80
5.6	38	9.6	81
5.7	39	9.7	83
5.8	40	9.8	84
5.9	41	9.9	85
6.0	42	10.0	86
6.1	43	10.1	87
6.2	44	10.2	88
6.3	45	10.3	89
6.4	46	10.4	90
6.5	48	10.5	91
6.6	49	10.6	92
6.7	50	10.7	93
6.8	51	10.8	95
6.9	52	10.9	96
7.0	53	11.0	97
7.1	54	11.1	98
7.2	55	11.2	99
7.3	56	11.3	100
7.4	57	11.4	101
7.5	58	11.5	102
7.6	60	11.6	103
7.7	61	11.7	104
7.8	62	11.8	105
7.9	63	11.9	107
		12.0	108

Annex 3

Expressions of urinary protein concentration and their approximate equivalents and clinical correlates

	Dipstick reading	Urine protein: creatinine ratio, mg/mmol (PCR)	Urine total protein excretion, (g/24 hour)	Urinary albumin: creatinine ratio, mg/mmol (ACR)	Urinary albumin excretion, micrograms/min (mg/24 hour)
Normal	Negative	< 15	< 0.150	< 2.5 (males) < 3.5 (females)	< 20 (< 30)
Microalbuminuria	Negative	< 15	< 0.150	≥ 2.5 to 30 (males)	20-200 (30-300)
“Trace” protein	Trace	15-44	0.150– 0.449	≥ 3.5 to 30 (females)	
Clinical proteinuria (macroalbuminuria)	1 +	45-149	0.450- 1.499	> 30	> 200 (> 300)
Nephrotic range proteinuria	2 +	150-449	1.50-4.49		
	3 +	≥ 450	≥ 4.50		

Values in this table are based on an assumed average creatinine excretion of 10 mmol/day and an average urine volume of 1.5 l/day.

NB males and females have different thresholds for the diagnosis of microalbuminuria as a consequence of the lower urinary creatinine excretion in women.

There is no single value for the accurate conversion between ACR to PCR, however, at low levels of proteinuria (< 1 g/day), a rough conversion is that doubling the ACR gives the PCR. At proteinuria excretion rates of > 1 g/day, the relationship is more accurately represented by $1.3 \times \text{ACR} = \text{PCR}$.

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