
*The National Collaborating Centre
for Chronic Conditions*

Funded to produce guidelines for the NHS by NICE

TYPE 2 DIABETES

National clinical guideline for management
in primary and secondary care (update)

This is an update of the following
NICE (inherited) clinical guidelines on
Type 2 diabetes which were published in 2002:
E – retinopathy; F – renal disease; G – blood glucose;
H – management of blood pressure and blood lipids

Published by



**Royal College
of Physicians**

Setting higher medical standards

Royal College of Physicians

The Royal College of Physicians plays a leading role in the delivery of high-quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 20,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

National Collaborating Centre for Chronic Conditions

The National Collaborating Centre for Chronic Conditions (NCC-CC) is a collaborative, multiprofessional centre undertaking commissions to develop clinical guidance for the National Health Service (NHS) in England and Wales. The NCC-CC was established in 2001. It is an independent body, housed within the Clinical Standards Department at the Royal College of Physicians of London. The NCC-CC is funded by the National Institute for Health and Clinical Excellence (NICE) to undertake commissions for national clinical guidelines on an annual rolling programme.

Citation for this document

National Collaborating Centre for Chronic Conditions. *Type 2 diabetes: national clinical guideline for management in primary and secondary care (update)*. London: Royal College of Physicians, 2008.

ISBN 978-1-86016-333-3

ROYAL COLLEGE OF PHYSICIANS
11 St Andrews Place, London NW1 4LE
www.rcplondon.ac.uk

Registered charity No 210508

Copyright © 2008 Royal College of Physicians of London

All rights reserved. No part of this publication may be reproduced in any form (including photocopying or storing it in any medium by electronic means and whether or not transiently or incidentally to some other use of this publication) without the written permission of the copyright owner. Applications for the copyright owner's written permission to reproduce any part of this publication should be addressed to the publisher.

Typeset by Dan-Set Graphics, Telford, Shropshire

Printed in Great Britain by The Lavenham Press Ltd, Sudbury, Suffolk

Contents

	Members of the Guideline Development Group	v
	Acknowledgements	vii
	Preface	viii
	DEVELOPMENT OF THE GUIDELINE	
1	Introduction	
1.1	Background	3
1.2	Definition	4
1.3	Prevalence	4
1.4	Health and resource burden	5
2	Methodology	
2.1	Aim	7
2.2	Scope	7
2.3	Audience	7
2.4	Involvement of people with Type 2 diabetes	8
2.5	Guideline limitations	8
2.6	Other work relevant to the guideline	8
2.7	Background	9
2.8	The process of guideline development	10
2.9	Disclaimer	14
2.10	Funding	14
3	Key messages of the guideline	
3.1	Key priorities for implementation	15
3.2	Algorithms	16
4	Glossary and definitions	19
	THE GUIDELINE	
5	Education	
5.1	Structured education	27
6	Lifestyle management/non-pharmacological management	
6.1	Dietary advice	31
6.2	Management of depression	39
7	Glucose control levels	
7.1	Clinical monitoring of blood glucose control	41
8	Self-monitoring of plasma glucose	47
9	Oral glucose control therapies (1): metformin, insulin secretagogues, and acarbose	
9.1	Clinical introduction	53
9.2	Metformin	53

9.3	Insulin secretagogues	65
9.4	Acarbose	79
9.5	Oral glucose control therapies; from evidence to recommendations	85
10	Oral glucose control therapies (2): other oral agents and exenatide	
10.1	Clinical introduction	89
10.2	Thiazolidinediones (glitazones)	89
10.3	Gliptins (GLP-1 enhancers): dipeptidyl peptidase 4 inhibitors (DPP-4 inhibitors)	114
10.4	Exenatide: GLP-1 mimetics	114
10.5	Oral glucose control therapies (2): other oral agents and exenatide; from evidence to recommendations	120
11	Glucose control: insulin therapy	
11.1	Oral agent combination therapy with insulin	125
11.2	Insulin therapy	130
11.3	Insulin detemir	146
11.4	Insulin delivery devices	146
12	Blood pressure therapy	
12.1	Clinical introduction	151
12.2	Blood pressure lowering – targets and intervention levels	151
12.3	Blood pressure lowering medications	157
13	Cardiovascular risk estimation	181
14	Management of blood lipid levels	
14.1	Overall clinical introduction	191
14.2	Targets and intervention levels	191
14.3	Statins and ezetimibe	193
14.4	Fibrates	198
14.5	Nicotinic acid and derivatives	205
14.6	Omega 3 fish oils	209
15	Antithrombotic therapy	
15.1	Antiplatelet therapy	215
16	Kidney damage	
16.1	Diabetes kidney disease management	223
17	Eye damage	233
18	Nerve damage	
18.1	Diabetic neuropathic pain management	235
18.2	Autonomic neuropathy	246
18.3	Gastroparesis	247
18.4	Erectile dysfunction	250
18.5	Other aspects of autonomic neuropathy	255
19	Areas for future research	257
	REFERENCES	259

Members of the Guideline Development Group

Professor Jonathan Mant (*Chair*)

Professor of Primary Care Stroke Research, University of Birmingham

Mrs Lina Bakhshi

Information Scientist, NCC-CC

Mrs Margaret Bannister

Nurse Consultant in Diabetes Care, Bradford and Airedale Primary Care Trust

Mrs Katherine Cullen

Health Economist, NCC-CC

Professor Melanie Davies

Professor of Diabetes Medicine, University of Leicester

Dr Jose Diaz

Health Services Research Fellow in Guideline Development, NCC-CC

Mrs Barbara Elster

Patient and Carer Representative, Essex

Dr Roger Gadsby

General Practitioner and Senior Lecturer in Primary Care, Warwickshire

Dr Anupam Garrib

Health Services Research Fellow, NCC-CC

Ms Irene Gummerson

Primary Care Pharmacist, Yorkshire

Dr Martin Hadley-Brown

General Practitioner Trainer, University of Cambridge

Professor Philip Home

Clinical Advisor to the GDG; Professor of Diabetes Medicine, Newcastle University

Mrs Kathryn Leivesley

Practice Nurse, North Manchester Primary Care Trust

Mrs Emma Marcus

Clinical Specialist Diabetes Dietitian, Hinckley and Bosworth Primary Care Trust

Mr Leo Nherera

Health Economist, National Collaborating Centre for Women's and Children's Health

Ms Roberta Richey

Health Services Research Fellow in Guideline Development, NCC-CC

Mr John Roberts

Patient and Carer Representative, Merseyside

Dr Mark Savage

Consultant Physician, North Manchester General Hospital

Lorraine Shaw

Paediatric Diabetes Clinical Nurse Specialist, Birmingham Children's Hospital

Dr Stuart Smelie

Consultant Chemical Pathologist, Bishop Auckland General Hospital

Ms Nicole Stack

Guideline Development Project Manager, NCC-CC

Ms Claire Turner

Guideline Development Senior Project Manager, NCC-CC

Ms Susan Varney

Health Services Research Fellow in Guideline Development, NCC-CC

Dr Jiten Vora

Consultant Physician Endocrinologist, Royal Liverpool and Broadgreen University Hospital

The following experts were invited to attend specific meetings and to advise the Guideline Development Group:

Dr Julian Barth

Consultant Chemical Pathologist, Leeds NHS Trust attended one meeting as a deputy for Dr Stuart Smellie

Dr Indranil Dasgupta

Consultant Physician and Nephrologist, Birmingham Heartlands Hospital

Dr Michael Feher

Consultant Physician, Chelsea Westminster Hospital attended one meeting as a deputy for Dr Mark Savage

Dr Charles Fox

Consultant Physician, Northampton General Trust attended one meeting as a deputy for Professor Melanie Davies

Natasha Jacques

Principal Pharmacist Medicine, Solihull Hospital attended one meeting as a deputy for Ms Irene Gummerson

Dr Eric Kilpatrick

Consultant Chemical Pathologist, University of Hull attended one meeting as a deputy for Dr Stuart Smellie

Dr Ian Lawrence

Consultant Diabetologist, University of Leicester attended one meeting as a deputy for Professor Melanie Davies and Dr Jiten Vora

Professor Sally Marshall

Professor of Diabetes, Newcastle University

Professor David Wood

Professor of Cardiovascular Medicine, Imperial College London

Acknowledgements

The Guideline Development Group (GDG) is grateful to Bernard Higgins, Jane Ingham, Rob Grant, Jill Parnham and Susan Tann of the NCC-CC for their support throughout the development of the guideline.

The GDG would like to thank the following individuals for giving their time to advise us regarding the design and interpretation of the economic model of analysis of third-line therapy with insulins, glitazones or exenatide in Type 2 diabetes:

- Professor Alastair Gray, University of Oxford
- Dr Philip Clarke, University of Sydney
- Dr Joanne Lord, National Institute for Health and Clinical Excellence.

The GDG would like to thank the following individuals for peer reviewing the guideline:

- Professor Simon Heller, University of Sheffield
- Professor David Owens, Llandough Hospital, Penarth
- Professor Bryan Williams, University of Leicester
- Dr Miles Fisher, Glasgow Royal Infirmary
- Professor Solomon Tesfaye, University of Sheffield
- Mr Irvine Turner, Patient Representative.

Preface

In 2007, the Centers for Disease Control and Prevention in the USA took the step, unusual for a non-infectious disease, of classifying the increase in the incidence of diabetes as an epidemic, their projections suggesting that the prevalence of this already common disease will have doubled by 2050. In the UK, diabetes already affects approximately 1.9 million adults overall, and some estimates suggest that there are an additional 0.5 million with undiagnosed diabetes.* This makes diabetes one of the commonest of all chronic medical conditions, and represents a huge potential problem for our health services.

Over 90% of people with diabetes have Type 2 diabetes. This is still perceived as the milder form, and while this may be true in some respects, such as the risk of ketoacidosis, the causation of Type 2 diabetes is more complex and the management is not necessarily easier. Type 2 diabetes can cause severe complications, affecting the eye, the nervous system and the kidney. The overall risk of cardiovascular disease is more than doubled, and life expectancy is reduced by an average 7 years. In 2002, NICE published a suite of five guidelines dealing with different aspects of the care of Type 2 diabetes. The rising prevalence of the disease, and the range of complications which can arise, reinforce the importance of up-to-date guidance and accordingly NICE have asked the National Collaborating Centre for Chronic Conditions (NCC-CC) to produce this guideline, amalgamating and updating the previously published work.

The guideline is informed by extensive literature and covers many aspects of diabetes management, although it is not intended to be a comprehensive textbook. It covers those topics of particular relevance to life expectancy such as control of cholesterol and lipid levels, and management of hypertension. It deals with major complications such as renal disease. There are also key recommendations in areas of great importance to patients such as structured education and the monitoring of glucose levels. Naturally, there are also sections dealing with control of blood glucose levels and the use of the various drugs available for this purpose.

The guideline development group (GDG) have had a particularly difficult task during development. The remit they were given was unusually large, and I have already mentioned the vast amount of evidence which they were required to consider. They were required to incorporate several existing NICE technology appraisals (TAs) within the guideline. In addition, they had to contend with a major safety scare over one of the glucose lowering agents which evolved over the course of guideline development. It is a measure of their commitment and appetite for hard work that, despite the size of the existing task, they were frustrated rather than relieved at not being able to include information about newer agents such as the DPP-4 inhibitors, the first of which was licensed towards the end of the development process (these agents will be covered at a later date in a separate, short guideline). All at the NCC-CC are extremely grateful to the GDG for the tremendous effort they have put into producing this guideline on schedule. The challenge now is to implement its recommendations and to make a genuine difference to the well-being and health of those with Type 2 diabetes.

Dr Bernard Higgins MD FRCP

Director, National Collaborating Centre for Chronic Conditions

* Department of Health. *Health survey for England 2003*. London: Stationary Office, 2004.

DEVELOPMENT OF THE GUIDELINE

1 Introduction

1.1 Background

Diabetes is a group of disorders with a number of common features, of which raised blood glucose is by definition the most evident. In England and Wales the four commonest types of diabetes are:

- Type 1 diabetes
- Type 2 diabetes
- secondary diabetes (from pancreatic damage, hepatic cirrhosis, endocrinological disease/therapy, or anti-viral/anti-psychotic therapy)
- gestational diabetes (diabetes of pregnancy).

This guideline is concerned only with Type 2 diabetes. The underlying disorder is usually that of a background of insulin insensitivity plus a failure of pancreatic insulin secretion to compensate for this.

The insulin insensitivity is usually evidenced by excess body weight or obesity, and exacerbated by overeating and inactivity. It is commonly associated with raised blood pressure, a disturbance of blood lipid levels, and a tendency to thrombosis. This combination is often recognised as the 'metabolic syndrome', and is associated with fatty liver and abdominal adiposity (increased waist circumference).

The insulin deficiency is progressive over time, such that the high glucose levels usually worsen relentlessly over a timescale of years, requiring continued escalation of blood glucose lowering therapy. The worsening insulin deficiency with age also means that diabetes can appear in elderly people who are quite thin. In some people in middle age the condition can be difficult to distinguish from slow onset Type 1 diabetes.

In people whose hyperglycaemia has yet to be treated, glucose metabolism may be sufficiently disturbed to cause symptoms, typically of polyuria, thirst, weight loss and fatigue. Diabetic coma (ketoacidosis) is uncommon in Type 2 diabetes unless exacerbating factors (infection, drugs) are present, but insulin deficiency and high sugar intake can lead to a related state (hyperosmolar coma).

Type 2 diabetes is notable for the increased cardiovascular risk that it carries. This can be manifest as coronary artery disease (heart attacks, angina), peripheral artery disease (leg claudication, gangrene), and carotid artery disease (strokes, dementia). Many people with Type 2 diabetes have the same risk of a cardiovascular event as someone without diabetes who has already had their first heart attack; people with diabetes and a previous cardiovascular event are at very high risk – around 10 times the background population. Accordingly management of cardiovascular risk factors plays a large part in care of people with Type 2 diabetes, and is particularly cost effective.

Because of the problems of maintaining good blood glucose control associated with the increasing insulin deficiency, the degree of hyperglycaemia occurring in some individuals is sufficient to give rise to a risk of the specific ('microvascular') complications of diabetes. Due

to early death caused by cardiovascular disease these are less common than in people with Type 1 diabetes, but include eye damage (sometimes blindness), kidney damage (sometimes requiring dialysis or transplantation), and nerve damage (resulting in amputation, painful symptoms, erectile dysfunction, and other problems).

This situation of multiple vascular risk factors and multiple complications leads to multiple targets for reduction of risk and improvement of health in people with Type 2 diabetes. Such targets for management include obesity, activity levels, plasma glucose control, blood pressure control, blood lipid control, reduction of thrombogenicity, laser therapy for eye damage, drug therapy to delay kidney damage, local foot care, and symptomatic treatments for various types of nerve damage. As a result diabetes care is typically complex and time consuming.

The necessary lifestyle changes, the complexities of management, and the side effects of therapy, together make self-monitoring and education for people with diabetes central parts of management.

1.2 Definition

The GDG worked to the World Health Organization (WHO) definition of diabetes, which requires a degree of high plasma glucose levels sufficient to put the individual at risk of the specific (microvascular) complications of diabetes. Diagnosis is not addressed in this guideline. This definition was reconfirmed by the WHO in 2006, but, like earlier versions, does not contain a specific definition for Type 2 diabetes.²

People are normally thought to have Type 2 diabetes if they do not have Type 1 diabetes (rapid onset, often in childhood, insulin-dependent, ketoacidosis if neglected) or other medical conditions or treatment suggestive of secondary diabetes. However, there can be uncertainty in the diagnosis particularly in overweight people of younger age. A further area of confusion is the group of disorders classified as monogenetic diabetes – formally Maturity Onset Diabetes of the Young (MODY) – which are usually not insulin requiring but which present in the first decades of life.

It is noted that Type 1 diabetes with onset after childhood can be confused with Type 2 diabetes. However, lower body weight, more rapid progression to insulin therapy, and absence of features of the metabolic syndrome often give useful distinguishing clues.

1.3 Prevalence

The prevalence of diabetes in the UK is increasing as is the prevalence of obesity, decreased physical activity, but also increased longevity after diagnosis thanks to better cardiovascular risk protection. The current prevalence of Type 2 diabetes is unknown, and will vary with factors such as mix of ethnic groups and degree of social deprivation.

Table 1.1 The prevalence of doctor-diagnosed diabetes (2003)³

	Men (≥55 years)	Women (≥55 years)
General population (%)	4.3	3.4
Black Caribbean	10.0	8.4
Black African	5.0	2.1
Indian	10.1	5.9
Pakistani	7.3	8.6
Bangladeshi	8.2	5.2
Chinese	3.8	3.3
Irish	3.6	2.3

Prevalence estimates vary from around 3.5 to 5.0%, the third edition of the International Diabetes Federation (IDF) Atlas suggesting 4.0%, being 1.71 million in the 20- to 79-year-old age group, of whom it is conventional to assume 85% have Type 2 diabetes.⁴ Current prevalence estimates are a poor pointer to future burden of diabetes due to their continuing increase. The healthcare burden is also affected by the improved longevity of people with diabetes with better management, which means that overall they carry a larger burden of complications and insulin deficiency needing more complex care.

1.4 Health and resource burden

Type 2 diabetes can result in a wide range of complications (see above), with repercussions for both the individual patient and the NHS. The economic impact of this disease includes at least three factors:

- direct cost to the NHS and associated healthcare support services
- indirect cost to the economy, including the effects of early mortality and lost productivity
- personal impact of diabetes and subsequent complications on patients and their families.

Mortality attributed to people with diabetes is suggested as 4.2% of deaths in men and 7.7% of deaths in women in the UK. These are likely to be underestimates as deaths from vascular events such as stroke and myocardial infarction (MI) are notorious for under-recording of the underlying causative disease. In a population-based study in Cardiff, at a time when population prevalence was only 2.5%, deaths in people with diabetes accounted for over 10% of the total, with around 60% attributable to diabetes.⁵ Life years lost vary considerably with factors such as blood glucose, blood pressure and blood lipid control, and smoking, as well as age, and can be estimated by comparing United Kingdom Prospective Diabetes Study (UKPDS) risk engine estimates to UK government statistical tables. Typically a 60-year-old man, newly diagnosed and without existing arterial disease can expect to lose 8–10 years of life without proper management.

Type 2 diabetes

The direct cost of Type 2 diabetes to the NHS is unknown, as much is classified as cardiovascular or renal disease. However, with prevalence estimates of 3.5–5.0%, and healthcare costs double those of the background population or more, estimates of 7–12% of total NHS expenditure seem not unreasonable. The IDF Atlas notes that in industrialised countries healthcare costs in people with diabetes tend to be double those of the background population. This suggests a £2.8 billion attributable cost for the UK for 2007.⁴

2 Methodology

2.1 Aim

The aim of the National Collaborating Centre for Chronic Conditions (NCC-CC) is to provide a user-friendly, clinical, evidence-based guideline for the NHS in England and Wales that:

- offers best clinical advice for the management of Type 2 diabetes
- is based on best published clinical and economic evidence, alongside expert consensus
- takes into account patient choice and informed decision making
- defines the major components of NHS care provision for Type 2 diabetes
- details areas of uncertainty or controversy requiring further research
- provides a choice of guideline versions for differing audiences.

2.2 Scope

The guideline was developed in accordance with a scope, which detailed the remit of the guideline originating from the Department of Health (DH) and specified those aspects of Type 2 diabetes care to be included and excluded. The application of the guideline to children has not been excluded but we were not able to specifically search for paediatric literature due to volume of work. When health carers are applying these guidelines to children they need to use their clinical judgement in doing so. For further assistance with applying this guideline to children please refer to the British National Formulary (BNF) for children.⁶

Prior to the commencement of the guideline development, the scope was subjected to stakeholder consultation in accordance with processes established by the National Institute for Health and Clinical Excellence (NICE).¹ The full scope is shown in appendix B. Available at www.rcplondon.ac.uk/pubs/brochure.aspx?e=247

2.3 Audience

The guideline is intended for use by the following people or organisations:

- all healthcare professionals
- people with Type 2 diabetes and their parents and carers
- patient support groups
- commissioning organisations
- service providers.

2.4 Involvement of people with Type 2 diabetes

The NCC-CC was keen to ensure the views and preferences of people with Type 2 diabetes and their carers informed all stages of the guideline. This was achieved by:

- having two people with Type 2 diabetes as patient representatives on the GDG
- consulting the Patient and Public Involvement Programme (PIIP) housed within NICE during the pre-development (scoping) and final validation stages of the guideline project
- the inclusion of patient groups as registered stakeholders for the guideline.

2.5 Guideline limitations

The guideline has the following limitations.

- NICE clinical guidelines usually do not cover issues of service delivery, organisation or provision (unless specified in the remit from the DH).
- NICE is primarily concerned with health services and so recommendations are not provided for social services and the voluntary sector. However, the guideline may address important issues in how NHS clinicians interface with these other sectors.
- Generally, the guideline does not cover rare, complex, complicated or unusual conditions.
- Where a meta-analysis was available, generally the individual papers contained within were not appraised.
- It is not possible in the development of a clinical guideline to complete an extensive systematic literature review of all pharmacological toxicity, although NICE expect their guidelines to be read alongside the summaries of product characteristics (SPCs).

2.6 Other work relevant to the guideline

The guideline will update the following NICE technology appraisals (TAs) but only in relation to Type 2 diabetes:

- 'Guidance on the use of glitazones for the treatment of Type 2 diabetes', *NICE technology appraisal guidance* no. 63 (2003)
- 'Guidance on the use of patient-education models for diabetes', *NICE technology appraisal guidance* no. 60 (2003)
- 'Guidance on the use of long-acting insulin analogues for the treatment of diabetes – insulin glargine', *NICE technology appraisal guidance* no. 53 (2002).

Related NICE public health guidance:

- 'Smoking cessation services, including the use of pharmacotherapies, in primary care, pharmacies, local authorities and workplaces, with particular reference to manual working groups, pregnant smokers and hard to reach communities', *Public health programme guidance* no. PH010 (February 2008)
- 'Physical activity guidance for the Highways Agency, local authorities, primary care, pharmacists, health visitors and community nurses, schools, workplaces, the leisure and fitness industry and sports clubs', *Public health programme guidance* no. PH008 (January 2007).

Related NICE clinical guidelines:

- ‘Cardiovascular risk assessment: the modification of blood lipids for the primary and secondary prevention of cardiovascular disease’ (expected date of publication May 2008)
- ‘Diabetes in pregnancy: management of diabetes and its complications from pre-conception to the postnatal period’, *NICE clinical guideline* no. 63 (2008)
- ‘Hypertension: management of hypertension in adults in primary care’ (partial update of NICE CG18), *NICE clinical guideline* no. 34 (2006)
- ‘Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children’, *NICE clinical guideline* no. 43 (2006)
- ‘Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults’, *NICE clinical guideline* no. 15 (2004, to be reviewed 2008)
- ‘Type 2 diabetes: prevention and management of foot problems’, *NICE clinical guideline* no. 10 (2004).

Related TA guidance:

- ‘Guidance on the use of ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia’, *NICE technology appraisal guidance* no. 132 (2007)
- ‘Guidance on the use of statins for the prevention of cardiovascular events in patients at increased risk of developing cardiovascular disease or those with established cardiovascular disease’, *NICE technology appraisal guidance* no. 94 (2006)
- ‘Guidance on the use of inhaled insulin for the treatment of Type 1 and Type 2 diabetes’, *NICE technology appraisal guidance* no. 113 (2006)
- ‘Guidance on the use of clopidogrel and dipyridamole for the prevention of arteriosclerotic events’, *NICE technology appraisal guidance* no. 90 (2005)
- ‘Guidance on the use of the clinical effectiveness and cost effectiveness of insulin pump therapy’, *NICE technology appraisal guidance* no. 57 (2003).

2.7 Background

The development of this evidence-based clinical guideline draws upon the methods described by the NICE’s ‘Guideline development methods manual’¹ and the methodology pack⁷ specifically developed by the NCC-CC for each chronic condition guideline (see www.rcplondon.ac.uk/clinical-standards/ncc-cc/Pages/NCC-CC.aspx). The developers’ role and remit is summarised in table 2.1.

Table 2.1 Role and remit of the developers	
NCC-CC	<p>The NCC-CC was set up in 2001 and is housed within the Royal College of Physicians (RCP). The NCC-CC undertakes commissions received from NICE.</p> <p>A multiprofessional partners' board inclusive of patient groups and NHS management governs the NCC-CC.</p>
NCC-CC Technical Team	<p>The technical team met approximately two weeks before each GDG meeting and comprised the following members:</p> <ul style="list-style-type: none"> GDG Chair GDG Clinical Adviser Information Scientist Two Research Fellows Health Economist Project Manager.
GDG	<p>The GDG met monthly (June 2006 to July 2007) and comprised a multidisciplinary team of professionals and people with Type 2 diabetes who were supported by the technical team.</p> <p>The GDG membership details including patient representation and professional groups are detailed in the GDG membership table at the front of this guideline.</p>
Guideline Project Executive	<p>The Project Executive was involved in overseeing all phases of the guideline. It also reviewed the quality of the guideline and compliance with the DH remit and NICE scope.</p> <p>The Project Executive comprises:</p> <ul style="list-style-type: none"> NCC-CC Director NCC-CC Assistant Director NCC-CC Manager NICE Commissioning Manager Technical Team.
Formal consensus	<p>At the end of the guideline development process the GDG met to review and agree the guideline recommendations.</p>
<p>Members of the GDG declared any interests in accordance with the NICE technical manual.¹ A register is given in appendix D, available online at www.rcplondon.ac.uk/pubs/brochure.aspx?e=247</p>	

2.8 The process of guideline development

The basic steps in the process of producing a guideline are:

- developing clinical evidence-based questions
- systematically searching for the evidence
- critically appraising the evidence
- incorporating health economic evidence
- distilling and synthesising the evidence and writing recommendations
- grading the evidence statements
- agreeing the recommendations

- structuring and writing the guideline
- updating the guideline.

▷ Developing evidence-based questions

The technical team drafted a series of clinical questions that covered the guideline scope. The GDG and Project Executive refine and approve these questions, which are shown in appendix A. Available at www.rcplondon.ac.uk/pubs/brochure.aspx?e=247

▷ Searching for the evidence

The information scientist developed a search strategy for each question. Key words for the search were identified by the GDG. In addition, the health economist searched for additional papers providing economic evidence or to inform detailed health economic work (for example, modelling). Papers that were published or accepted for publication in peer-reviewed journals were considered as evidence by the GDG. Conference paper abstracts and non-English language papers were excluded from the searches.

Each clinical question dictated the appropriate study design that was prioritised in the search strategy but the strategy was not limited solely to these study types. The research fellow or health economist identified titles and abstracts from the search results that appeared to be relevant to the question. Exclusion lists were generated for each question together with the rationale for the exclusion. The exclusion lists were presented to the GDG. Full papers were obtained where relevant. See appendix A for literature search details. Available at www.rcplondon.ac.uk/pubs/brochure.aspx?e=247

▷ Appraising the evidence

The research fellow or health economist, as appropriate, critically appraised the full papers. In general, no formal contact was made with authors; however, there were ad hoc occasions when this was required in order to clarify specific details. Critical appraisal checklists were compiled for each full paper. One research fellow undertook the critical appraisal and data extraction. The evidence was considered carefully by the GDG for accuracy and completeness.

All procedures are fully compliant with the:

- NICE methodology as detailed in the ‘Guideline Development Methods – Information for National Collaborating Centres and Guideline Developers’ Manual¹
- NCC-CC quality assurance document and systematic review chart available at www.rcplondon.ac.uk/clinical-standards/ncc-cc/Pages/NCC-CC.aspx.

▷ Health economic evidence

Areas for health economic modelling were agreed by the GDG after the formation of the clinical questions. The health economist reviewed the clinical questions to consider the potential application of health economic modelling, and these priorities were agreed with the GDG.

The health economist performed supplemental literature searches to obtain additional data for modelling. Assumptions and designs of the models were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

▷ Distilling and synthesising the evidence and developing recommendations

The evidence from each full paper was distilled into an evidence table and synthesised into evidence statements before being presented to the GDG. This evidence was then reviewed by the GDG and used as a basis upon which to formulate recommendations. The criteria for grading evidence are shown in table 2.2.

Evidence tables are available online at www.rcplondon.ac.uk/pubs/brochure.aspx?e=247

▷ Grading the evidence statements

Level of evidence	Type 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 of RCTs, or RCTs with a low risk of bias.
1–	Meta-analyses, systematic reviews of RCTs, 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, bias or chance and a high probability that the relationship is causal.
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal.
2–	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal.*
3	Non-analytic studies (for example case reports, case series).
4	Expert opinion, formal consensus.

*Studies with a level of evidence ‘–’ are not used as a basis for making a recommendation.
RCT, randomised controlled trial

▷ Agreeing the recommendations

The GDG employed formal consensus techniques to:

- ensure that the recommendations reflected the evidence base
- approve recommendations based on lesser evidence or extrapolations from other situations
- reach consensus recommendations where the evidence was inadequate
- debate areas of disagreement and finalise recommendations.

The GDG also reached agreement on the following:

- five recommendations as key priorities for implementation
- five key research recommendations
- algorithms.

In prioritising key recommendations for implementation, the GDG took into account the following criteria:

- high clinical impact
- high impact on reducing variation
- more efficient use of NHS resources
- allowing the patient to reach critical points in the care pathway more quickly.

Audit criteria for this guideline will be produced for NICE by Clinical Accountability Service Planning and Evaluation (CASPE) Research following publication in order to provide suggestions of areas for audit in line with the key recommendations for implementation.

▷ Structuring and writing the guideline

The guideline is divided into sections for ease of reading. For each section the layout is similar and contains the following parts.

- *Clinical introduction* sets a succinct background and describes the current clinical context.
- *Methodological introduction* describes any issues or limitations that were apparent when reading the evidence base.
- *Evidence statements* provide a synthesis of the evidence base and usually describes what the evidence showed in relation to the outcomes of interest.
- *Health economics* presents, where appropriate, an overview of the cost effectiveness evidence base, or any economic modelling.
- *From evidence to recommendations* sets out the GDG decision-making rationale providing a clear and explicit audit trail from the evidence to the evolution of the recommendations.
- *Recommendations* provide stand alone, action-orientated recommendations.
- *Evidence tables* are not published as part of the full guideline but are available online at www.rcplondon.ac.uk/pubs/brochure.aspx?e=247. These describe comprehensive details of the primary evidence that was considered during the writing of each section.

▷ Writing the guideline

The first draft version of the guideline was drawn up by the technical team in accord with the decisions of the GDG, incorporating contributions from individual GDG members in their expert areas and edited for consistency of style and terminology. The guideline was then submitted for a formal public and stakeholder consultation prior to publication. The registered stakeholders for this guideline are detailed on the NICE website, www.nice.org.uk. Editorial responsibility for the full guideline rests with the GDG.

Table 2.3 Versions of this guideline	
Full version	Details the recommendations, the supporting evidence base and the expert considerations of the GDG. Published by the NCC-CC. Available at www.rcplondon.ac.uk/pubs/brochure.aspx?e=247
NICE version	Documents the recommendations without any supporting evidence. Available at www.nice.org.uk
'Quick reference guide'	An abridged version. Available at www.nice.org.uk
'Understanding NICE guidance'	A lay version of the guideline recommendations. Available at www.nice.org.uk

▷ Updating the guideline

Literature searches were repeated for all of the evidence-based questions at the end of the GDG development process allowing any relevant papers published up until 16 April 2007 to be considered. Future guideline updates will consider evidence published after this cut-off date.

Two years after publication of the guideline, NICE will ask a National Collaborating Centre to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an early update. If not, the guideline will be considered for update approximately 4 years after publication.

2.9 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The NCC-CC disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

2.10 Funding

The NCC-CC was commissioned by NICE to undertake the work on this guideline.

3 Key messages of the guideline

3.1 Key priorities for implementation

Offer structured education to every person and/or their carer at and around the time of diagnosis, with annual reinforcement and review. Inform people and their carers that structured education is an integral part of diabetes care.

Provide individualised and ongoing nutritional advice from a healthcare professional with specific expertise and competencies in nutrition.

When setting a target glycated haemoglobin (GHb):

- involve the person in decisions about their individual HbA_{1c} target level, which may be above that of 6.5 % set for people with Type 2 diabetes in general
- encourage the person to maintain their individual target unless the resulting side effects (including hypoglycaemia) or their efforts to achieve this impair their quality of life
- offer therapy (lifestyle and medication) to help achieve and maintain the HbA_{1c} target level
- inform a person with a higher HbA_{1c} that any reduction in HbA_{1c} towards the agreed target is advantageous to future health
- avoid pursuing highly intensive management to levels of less than 6.5 %.

Offer self-monitoring of plasma glucose to a person newly diagnosed with Type 2 diabetes only as an integral part of his or her self-management education. Discuss its purpose and agree how it should be interpreted and acted upon.

When starting insulin therapy, use a structured programme employing active insulin dose titration that encompasses:

- structured education
- continuing telephone support
- frequent self-monitoring
- dose titration to target
- dietary understanding
- management of hypoglycaemia
- management of acute changes in plasma glucose control
- support from an appropriately trained and experienced healthcare professional.

3.2 Algorithms

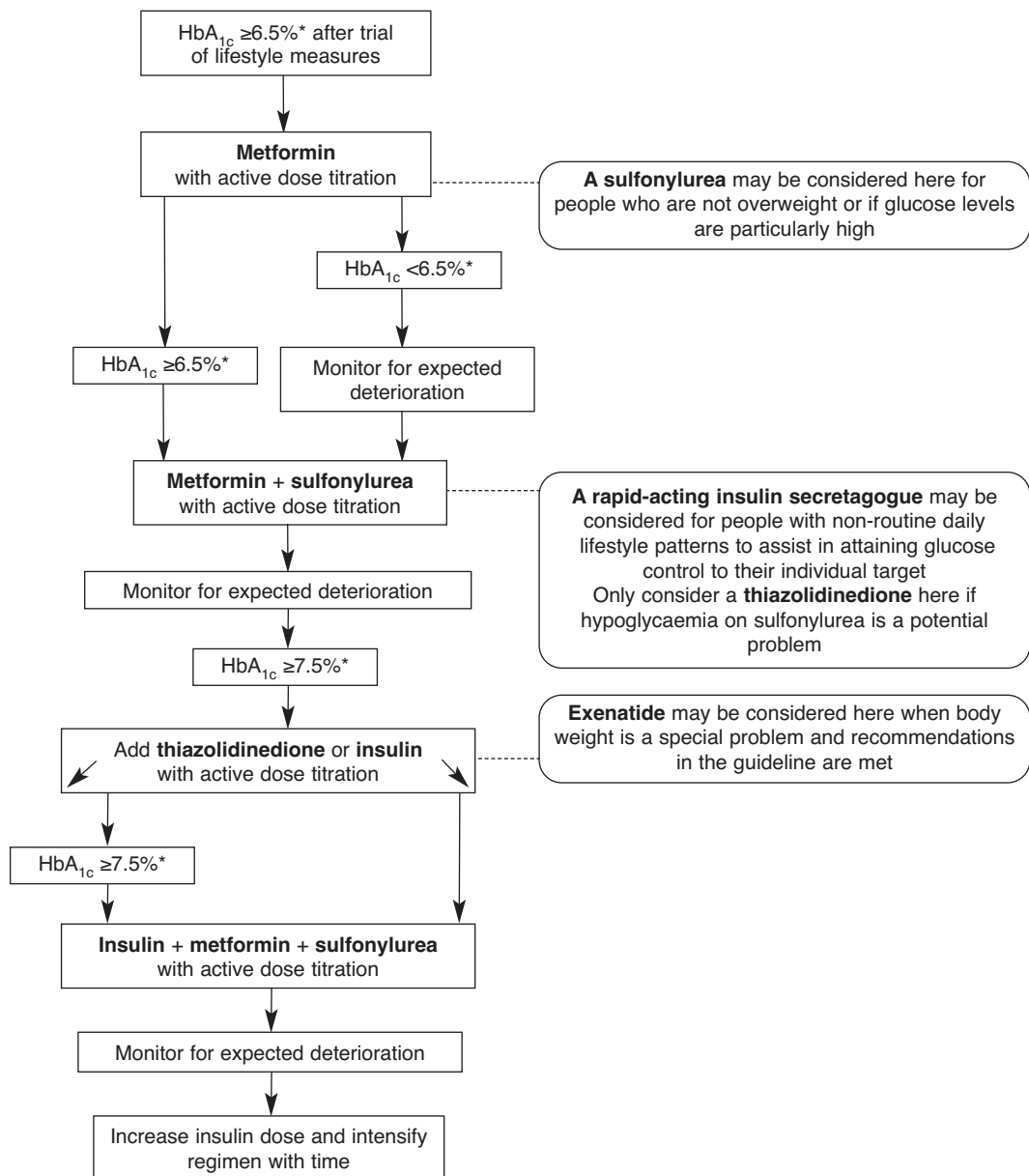


Figure 3.1 Scheme for the pharmacotherapy of glucose lowering in people with Type 2 diabetes
 For details see recommendations on glucose lowering targets, clinical monitoring, use of oral agents, and use of insulin
 * or as individually agreed

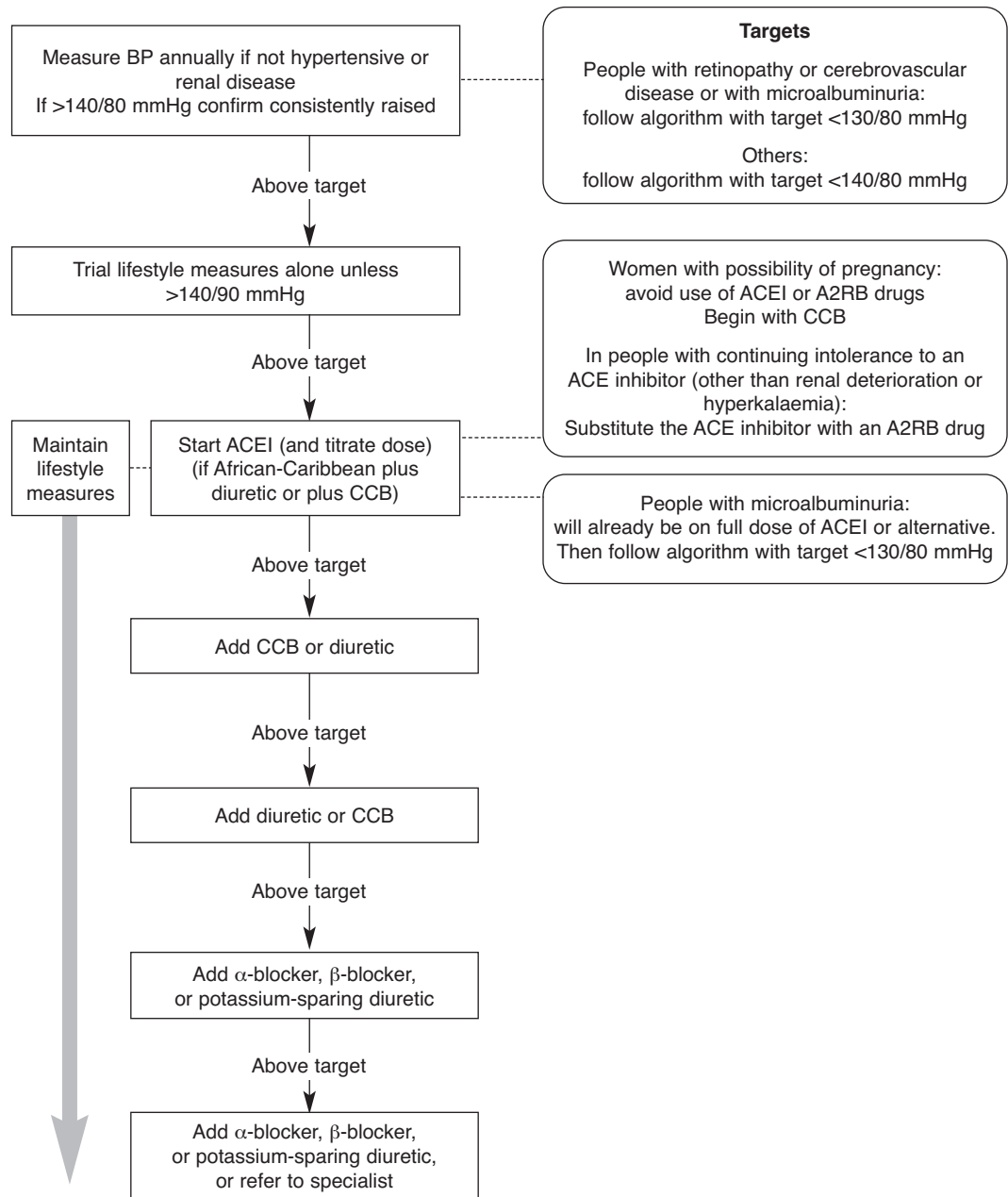


Figure 3.2 Scheme for the management of blood pressure (BP) for people with Type 2 diabetes

ACEI, angiotensin-converting enzyme inhibitor; A2RB, angiotensin 2 receptor blocker (sartan); CCB, calcium channel blocker

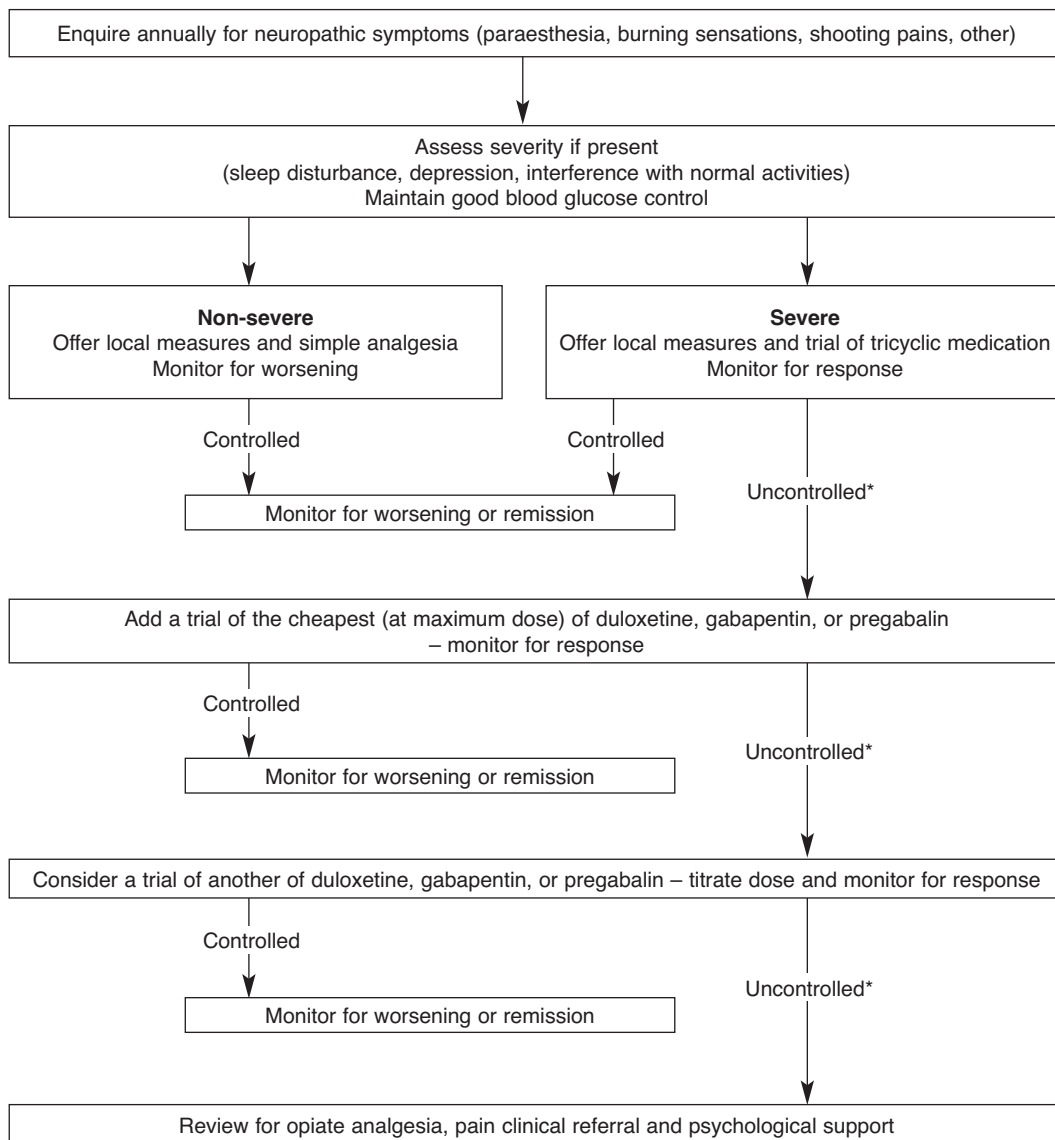


Figure 3.3 Diabetic symptomatic neuropathy management – a therapeutic summary

*Where neuropathic symptoms cannot be adequately controlled it is useful, to help individuals cope, to explain the reasons for the problem, the likelihood of remission in the medium term, the role of improved blood glucose control

4 Glossary and definitions

ACEI	Angiotensin-converting enzyme inhibitor
ACR	Albumin creatinine ratio
ADA	American Diabetes Association
AER	Albumin excretion rate – a measure of kidney damage due to diabetes (and other conditions) and a risk factor for arterial disease.
Albuminuria	The presence of albumin and other proteins in urine.
Alpha-glucosidase inhibitors	Group of drugs which inhibit the digestion of complex carbohydrates in the gut, and thus flatten the post-meal blood glucose excursion.
BMI	Body mass index – a index of body weight corrected for height.
Cohort study	A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.
CKD	Chronic kidney disease
Confidence interval (CI)	A range of values which contains the true value for the population with a stated ‘confidence’ (conventionally 95%). The interval is calculated from sample data, and generally straddles the sample estimate. The 95% confidence value means that if the study, and the method used to calculate the interval, is repeated many times, then 95% of the calculated intervals will actually contain the true value for the whole population.
Cochrane review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Concordance	Concordance is a concept reflecting the extent to which a course of action agreed between clinicians and a person with diabetes is actually carried out; often but not solely used in the sense of therapeutic interventions or behavioural changes.
Cost-effectiveness analysis	An economic study design in which consequences of different interventions are measured using a single outcome, usually in natural units (for example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
Cost-utility analysis	A form of cost-effectiveness analysis in which the units of effectiveness are quality adjusted life years.
DCCT	Diabetes Control and Complications Trial – a landmark study of the effects of intensification of diabetes care on development of microvascular complications.

Diabetes centre	A generic term for a source of a unified multidisciplinary diabetes service.
Diabetes mellitus	Chronic condition characterised by elevated blood glucose levels. Diabetes is of diverse aetiology and pathogenesis, and should not be regarded as a single disease. Predominant types are Type 1 diabetes and Type 2 diabetes, diabetes secondary to other pancreatic disease or other endocrine disease, and diabetes of onset in pregnancy.
Diabetes UK	Self-help charity for people with diabetes in the UK, and a professional organisation for diabetes care.
Education	In the context of this guideline, patient education in self-management of everyday diabetes issues like insulin therapy, dietary changes, self-monitoring of glucose level, physical exercise, coping with concurrent illness, how to avoid hypoglycaemia, complications, arterial risk control, jobs, travel, etc.
FBG	Fasting blood glucose level or concentration
FPG	Fasting plasma glucose level or concentration
Framingham equation	A widely known and used calculation of arterial risk, derived from a long-term study in Framingham, Massachusetts. Not valid in people with Type 1 or Type 2 diabetes.
GDG	Guideline Development Group
Glucose excursions	Change in blood glucose levels especially after meals.
GFR	Glomerular filtration rate – a measure of kidney function.
GHb	Glycated haemoglobin – see HbA _{1c} .
GI	Gastrointestinal
HbA_{1c}	The predominant form of glycated haemoglobin, present in red blood cells, and formed when the normal haemoglobin A reacts non-enzymatically with glucose. As the reaction is slow and only concentration dependent, the amount of HbA _{1c} formed is proportional only to the concentration of HbA and glucose. As HbA remains in the circulation for around 3 months, the amount of HbA _{1c} present, expressed as a percentage of HbA, is proportional to the glucose concentration over that time.
HTA	Health Technology Assessment, funded by the NHS Research and Development Directorate.
IDF	International Diabetes Federation – a global federation of diabetes associations.
Incremental cost	The cost of one alternative less the cost of another.
Incremental cost effectiveness ratio (ICER)	The ratio of the difference in costs between two alternatives to the difference in effectiveness between the same two alternatives.
Insulin analogues	A derivative of human insulin in which change of the amino-acid sequence alters duration of action after injection.

Insulin regimen	A therapeutic combination of different insulin preparations, including time of injection and frequency during a day.
IHD	Ischaemic heart disease
Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result.
Metabolic syndrome	Overweight (abdominal adiposity), insulin insensitivity, higher blood pressure, abnormal blood fat profile.
Methodological limitations	Features of the design or reporting of a clinical study which are known to be associated with risk of bias or lack of validity. Where a study is reported in this guideline as having significant methodological limitations, a recommendation has not been directly derived from it.
MI	Myocardial infarction
Microalbuminuria	A low but clinically significant level of albumin and other proteins in the urine.
NCC-CC	The National Collaborating Centre for Chronic Conditions, set up in 2000 to undertake commissions from the NICE to develop clinical guidelines for the NHS.
NHS	National Health Service – this guideline is written for the NHS in England and Wales.
NICE	National Institute for Health and Clinical Excellence – a special health authority set up within the NHS to develop appropriate and consistent advice on healthcare technologies, and to commission evidence-based guidelines.
NPH insulin	Neutral protamine Hagedorn insulin – a basal insulin, named after the Danish researcher Hans Christian Hagedorn, and developed in the 1940s. Synonymous with isophane insulin.
NS	Not significant (at the 5% level unless stated otherwise).
NSC	National Screening Committee (UK)
NSF	National Service Framework – a nationwide initiative designed to improve delivery of care for a related group of conditions.
Observational study	Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups, for example cohort studies and case-control studies.
Odds ratio	A measure of relative treatment effectiveness. An odds ratio of 1 means equality between the comparisons in the study, and higher numbers mean greater differences. The odds of an event happening in the intervention group, divided by the odds of it happening in the control group.
PDE5 inhibitors	Phosphodiesterase type 5 inhibitors, a class of drugs developed in recent years to treat erectile dysfunction.

PROCAM	Prospective Cardiovascular Münster Heart Study – an epidemiological study performed in Germany.
Proteinuria	The presence of protein in the urine.
p-values	The probability that an observed difference could have occurred by chance. A p-value of less than 0.05 is conventionally considered to be ‘statistically significant’.
Quality of life	A term used to describe an individual’s level of satisfaction with their life and general sense of well-being. It is often measured as physical, psychological and social well-being.
Quality of life-adjusted year (QALY)	A measure of health outcome which assigns to each period of time a weight, ranging from 0 to 1, corresponding to the health-related quality of life during that period, where a weight of 1 corresponds to optimal health, and a weight of 0 corresponds to a health state judged equivalent to death; these are then aggregated across time periods.
RCT	Randomised controlled trial. A trial in which people are randomly assigned to two (or more) groups – one (the experimental group) receiving the treatment that is being tested, and the other (the comparison or control group) receiving an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. Such trial designs help minimise experimental bias.
RR	Relative risk
Sensitivity analysis	A measure of the extent to which small changes in parameters and variables affect a result calculated from them. In this guideline, sensitivity analysis is used in health economic modelling.
Short-form 36 (SF-36)	The SF-36 assesses functioning and well-being in chronic disease. Thirty-six items in eight domains are included, which cover functional status, well-being, and overall evaluation of health.
Specialist	A clinician whose practice is limited to a particular branch of medicine or surgery, especially one who is certified by a higher medical educational organisation.
Stakeholder	Any national organisation, including patient and carers’ groups, healthcare professionals and commercial companies with an interest in the guideline under development.
Statistical significance	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p < 0.05$).
Systematic review	Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.

Technology appraisal	Formal ascertainment and review of the evidence surrounding a health technology, restricted in the current document to appraisals undertaken by NICE.
Thiazolidinediones	A group of drugs which improve insulin sensitivity in people with reduced sensitivity to their own or injected insulin; presently the licensed drugs are both of the chemical group known as trivially 'glitazones' or PPAR- γ agonists.
Type 1 diabetes	Insulin-deficiency disease, developing predominantly in childhood, characterised by hyperglycaemia if untreated, and with a consequent high risk of vascular damage usually developing over a period of decades.
Type 2 diabetes	Diabetes generally of slow onset mainly found in adults and in association with features of the metabolic syndrome. Carries a very high risk of vascular disease. While not insulin dependent many people with the condition eventually require insulin therapy for optimal blood glucose control.
UAER	Urinary albumin excretion rate
UKPDS	United Kingdom Prospective Diabetes Study – a landmark study of the effect of different diabetes therapies on vascular complications in people with Type 2 diabetes.
WHO	World Health Organization

THE GUIDELINE

5 Education

5.1 Structured education

5.1.1 Clinical introduction

Type 2 diabetes mellitus is a progressive long-term medical condition that is predominantly managed by the person with the diabetes and/or their carer as part of their daily life. Accordingly, understanding of diabetes, informed choice of management opportunities, and the acquisition of relevant skills for successful self-management play an important role in achieving optimal outcomes. Delivery of these needs is not always assured by conventional clinical consultations. Structured programmes have been designed not only to improve people's knowledge and skills, but also to help motivate and sustain people with diabetes in taking control of their condition and in delivering effective self-management.

Recent information from the Health Commission survey in 2007 suggests that only 11% of people with Type 2 diabetes report being offered structured education.⁸ This suggests that the majority of healthcare providers have found it difficult to implement and resource quality education programmes that meet these standards. There appears to be an urgent need to ensure that all people with Type 2 diabetes are offered high-quality structured education. The aims of structured education and self-management programmes are to improve outcomes through addressing the individual's health beliefs, optimising metabolic control, addressing cardiovascular risk factors (helping to reduce the risk of complications), facilitating behaviour change (such as increased physical activity), improving quality of life and reducing depression. An effective programme will also enhance the relationship between the person with diabetes and their healthcare professionals, thereby providing the basis of true partnership in diabetes management.

The clinical question that has been addressed is how to deliver such education, including what approaches deliver the intended benefits, and what components of the education process best deliver the surrogate, self-care, and quality of life outcomes.

5.1.2 Methodological introduction and evidence statements

Please refer to the Technology Assessment Report 'The clinical effectiveness of diabetes education models for Type 2 diabetes: a systematic review' commissioned by the NHS R&D Health Technology Assessment (HTA) programme on behalf of the NCC-CC. Available at www.nchta.org/project/1550.asp

5.1.3 Health economic methodological introduction

Two papers were identified in the search for health economics. Neither study was conducted in the UK and the results were not generalisable to the UK setting so both were excluded.^{9,10}

5.1.4 From evidence to recommendations

The GDG noted that the last review of this area by a HTA on behalf of NICE in 2003 looked at the evidence for structured education. Little robust evidence of the effectiveness of any

particular educational approach for people with Type 2 diabetes was found. One conclusion was that further research was required, but meanwhile that educational programmes with a theoretical basis demonstrated improved outcomes, and that group education was a more effective use of resources and may have additional benefits.

Educational interventions are not only complex in themselves, but they also exist in a complex environment with other aspects of managing a chronic disease. Such interventions will interact with, and support medical management directed at vascular risk factors and that of diabetes complications which have already developed. Their success is likely to depend on the individual's personal and cultural beliefs, the overall healthcare setting, their lifestyles, and perhaps their educational background.

It was noted that to address some of the difficulties in describing and implementing effective structured education and self-management programmes, a Patient Education Working Group (PEWG) had been convened by the Department of Health and Diabetes UK, and had laid out in detail the necessary requirements for developing high-quality patient education programmes. The key criteria had been endorsed by the recent HTA review. The five standards were as follows.

- 1 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 development of self-management attitudes, beliefs, knowledge and skills for the learner, their family and carers.
- 2 The programme should have a structured curriculum which is theory-driven, evidence-based, resource-effective, have supporting materials, and be written down.
- 3 It should be delivered by trained educators who should 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.
- 4 The programme itself should be quality assured, be reviewed by trained, competent, independent assessors and be assessed against key criteria to ensure sustained consistency.
- 5 The outcomes from the programme should be regularly audited.

The GDG found no reason to diverge from these principles. The GDG noted and endorsed the importance of quality assurance and audit in this complex area.

As the intervention is complex, the measured outcomes of any particular programme are by nature multifaceted and will vary with such factors as the timing in relation to diagnosis, critical changes of therapy, or other critical clinical findings. Even then, appropriate study outcomes are for the most part interim surrogate measures; no studies included late complications. However, psychological outcomes as well as biomedical outcomes can be appropriately assessed, to include quality of life and change in healthcare behaviours, and aspects of depressed mood. More directly cognitive measures, knowledge, acquisition of skills, and changing health beliefs were found to be useful indicators of a programme's effectiveness.

The HTA commissioned for the current review included 14 studies, of which eight appeared to have been conducted since 2003, and most were for people with established (rather than newly diagnosed) Type 2 diabetes. The GDG noted that, as expected, some studies showed effects on HbA_{1c}, others improved body weight and other lifestyle changes, some improved quality of life or knowledge, and yet others changed health beliefs or reduced depression. This diversity was often simply a reflection of study aims and design. The HTA review acknowledged that health

psychology approaches and some methods of health promotion have a good evidence base, but little is incorporated into studies of structured education, even though addressing health beliefs and motivating individuals to change behaviour is a cornerstone of any educational programme. Reported training for diabetes educators was poorly detailed in most studies.

The GDG was concerned that only three studies were UK-based. As cultural issues, patient health beliefs and attitudes are likely to differ from one country to another, applicability of the others may be limited. The GDG noted that the UK Diabetes Education and Self Management for Ongoing and Newly Diagnosed (DESMOND study) found changes in health beliefs, reduction in depression, and increases in self-reported physical activity, reduction in weight and improvement in smoking status. In people with established diabetes there was useful evidence from the X-PERT programme with improvements in HbA_{1c}, reduced diabetes medication, body weight, waist circumference, total serum cholesterol, diabetes knowledge and increase in self-reported physical activity and treatment satisfaction.

Overall the GDG then felt that well-designed and well-implemented programmes were likely to be effective and cost-effective interventions for people with Type 2 diabetes, in line with the NICE TA. For those people in whom education delivered in a group setting is appropriate, it is evidently likely to be more cost effective.

RECOMMENDATIONS

- R1 Offer structured education to every person and/or their carer at and around the time of diagnosis, with annual reinforcement and review. Inform people and their carers that structured education is an integral part of diabetes care.
- R2 Select a patient-education programme that meets the criteria laid down by the Department of Health and Diabetes UK Patient Education Working Group.
- Any programme should be evidence-based, and suit the needs of the individual. The programme should have specific aims and learning objectives, and should support development of self-management attitudes, beliefs, knowledge and skills for the learner, their family and carers.
 - The programme should have a structured curriculum that is theory-driven and evidence-based, resource-effective, has supporting materials, and is written down.
 - The programme should be delivered by trained educators who have an understanding of education theory appropriate to the age and needs of the programme learners, and are trained and competent in delivery of the principles and content of the programme they are offering.
 - The programme itself should be quality assured, and be reviewed by trained, competent, independent assessors who assess it against key criteria to ensure sustained consistency.
 - The outcomes from the programme should be regularly audited.
- R3 Ensure the patient education programme provides the necessary resources to support the educators, and that educators are properly trained and given time to develop and maintain their skills.
- R4 Offer group education programmes as the preferred option. Provide an alternative of equal standard for a person unable or unwilling to participate in group education.

Type 2 diabetes

- R5 Ensure the patient-education programmes available meet the cultural, linguistic, cognitive, and literacy needs within the locality.
- R6 Ensure all members of the diabetes healthcare team are familiar with the programmes of patient education available locally, that these programmes are integrated with the rest of the care pathway, and that people with diabetes and their carers have the opportunity to contribute to the design and provision of local programmes.

6 Lifestyle management/ non-pharmacological management

6.1 Dietary advice

6.1.1 Clinical introduction

All people with Type 2 diabetes should be supported to:

- try to achieve and maintain blood glucose levels and blood pressure in the normal range or as close to normal as is safely possible
- maintain a lipid and lipoprotein profile that reduces the risk of vascular disease.

Optimal dietary behaviours can contribute to all of these.

Dietary intervention should address the individual's nutritional needs, taking into account personal choices, cultural preferences and willingness to change, and to ensure that quality of life is optimised. It is usual that a registered dietician plays a key role in providing nutritional care advice within the multidisciplinary diabetes team. It is also recognised that all team members need to be knowledgeable about nutritional therapy, and give emphasis to consistent dietary and lifestyle advice.¹¹

The management of obesity is not specifically addressed in the current guideline. Readers are referred to the NICE obesity management guideline which addresses the area in some detail.¹²

Smoking cessation is not addressed in the current guideline. Readers are referred to the NICE public health programme guidance on smoking cessation services, including the use of pharmacotherapies, in primary care, pharmacies, local authorities and workplaces, with particular reference to manual working groups, pregnant smokers and hard to reach communities. Guidance was published in February 2008.

Clinical questions arise around the optimal strategies to reduce calorie intake (and thus improve sensitivity to endogenous insulin), to control exogenous delivery of free sugars into the circulation, to control blood pressure, and to optimise the blood lipid profile. Issues specifically related to people with kidney disease or of medical use of fish oils are not considered in this section. Issues specifically related to delivery of patient education are considered in the chapter on Patient Education (see chapter 5).

6.1.2 Methodological introduction

The search attempted to identify RCTs and observational studies conducted in adults with Type 2 diabetes which were assessing different forms of dietary advice targeting weight loss. A sample size threshold of N=50 and a follow-up of at least 3 months were established as cut-off points. Studies evaluating purely pharmacological interventions for weight reduction were excluded.

There were only eight studies that addressed this question.^{13–20} Two RCTs were excluded due to methodological limitations.* In all the studies, the intent was for participants to lose weight and thereby improve glycaemic, lipid and blood pressure control.** Among the remaining six studies there were four RCTs and two observational studies. No major methodological limitations were identified across these studies.

▷ RCTs

One RCT¹⁷ compared the effects of a combined intervention; low-calorie diet, sibutramine therapy and meal replacements with an individualised reduced calorie diet, and was the only study to include the use of weight-loss medication.

Two RCTs used the American Diabetes Association (ADA) guidelines as a comparison group to either a soy-based meal replacement intervention,¹³ N=104 with a 1-year follow-up, or a low-fat vegan diet,¹⁴ N=99 with a 22-week follow-up.

A further RCT compared a low-fat with a low-carbohydrate diet.¹⁶

▷ Observational studies

A case series with a follow-up of 6.5 years investigated the onset of diabetic complications and adherence to ADA recommendations.¹⁹ A prospective cohort study addressed the relationship between eating habits and long-term weight gain, following a group of patients being managed in primary care for a period of 4 years.²⁰

It should be noted that the results of diet interventions aimed at patients with Type 2 diabetes are difficult to interpret due to differences in the interventions, the populations, the study designs and the outcomes reported.

As is obvious, isolated diet interventions without adequate educational support and concomitant lifestyle changes are very unlikely to reduce risk factors and to improve clinical outcomes and quality of life for patients with Type 2 diabetes.

6.1.3 Health economic methodological introduction

No health economic papers were identified.

6.1.4 Evidence statements

▷ Weight reduction and glycaemic control outcomes

RCTs

Studies that compared a meal replacement intervention with a reduced calorie diet

An RCT comparing a soy-based meal replacement with an individualised diet based on ADA recommendations in obese Type 2 diabetics¹³ found that average weight reduction in the meal replacement group was greater than that in the individualised diet group. At 6 months, the meal

* One RCT comparing the effects of a high-protein with a low-protein diet¹⁵ and another RCT comparing low-carbohydrate versus conventional weight loss diets in severely obese adults.¹⁸

** Four studies focused on the effects of diet in obese Type 2 diabetics.

replacement group had lost on average 5.24 ± 0.60 kg, and the individualised diet group had lost an average of 2.85 ± 0.67 kg ($p=0.0031$). At 1 year this difference was not significant with the meal replacement group losing on average 4.35 ± 0.81 kg and the individualised diet group losing an average of 2.36 ± 0.76 kg ($p=0.0670$). **Level 1+**

The same RCT reported that similar changes were observed in the body mass index (BMI) at 12 months with a reduction of 1.47 ± 0.27 kg/m² in the meal replacement group and 0.77 ± 0.25 kg/m² in the individualised diet group. Although these values were significantly different from their baseline values, none were significantly different from each other ($p=0.0687$). **Level 1+**

With respect to glycaemic control, the RCT found that mean HbA_{1c} levels were significantly lower in the meal replacement than in the individualised diet group, $0.49 \pm 0.22\%$ ($p=0.0291$), for the entire study period. Plasma glucose concentrations were significantly lower in the meal replacement group than in the individualised diet group at 3 ($p=0.04$) and 6 ($p=0.002$) months, but not at 12 months ($p=0.595$). **Level 1+**

The study by Redmon¹⁷ reported on a combination intervention including sibutramine, an intermittent low-calorie diet with the use of meal replacements for 1 week every 2 months, and the use of meal replacements between the low-calorie diet weeks. The comparison group received an individualised diet plan with a 500–1,000 kcal energy deficit per day.

The study reported that at 1 year of follow-up, the combination therapy group had a significantly greater weight loss of 7.3 ± 1.3 kg than the standard therapy group 0.8 ± 0.9 kg ($p < 0.001$), with most weight loss occurring during the low-calorie weeks and some weight gain occurring in between the low-calorie weeks. **Level 1+**

In relation to glycaemic control, the study showed that at 1 year, HbA_{1c} had declined from a baseline of $8.1 \pm 0.2\%$ to $7.5 \pm 0.3\%$ in the combination therapy group but had remained unchanged at $8.2 \pm 0.2\%$ in the standard therapy group, and this difference was significant ($p=0.05$). After adjusting for medication changes, this difference remained significant. In an analysis of those participants whose medication had not changed, it was found that there was a significant positive linear association between change in weight at 1 year and change in HbA_{1c} ($r=0.53$; $p=0.006$). A 5 kg decrease in weight at 1 year was associated with a 0.4% decrease in HbA_{1c}. **Level 1+**

Studies comparing a low-carbohydrate with a low-fat diet

One RCT¹⁶ examined the short-term effects, participants were followed up for 3 months, of a low-carbohydrate diet compared with a reduced portion low-fat diet in obese Type 2 diabetics. There was a significantly larger mean weight reduction in the low-carbohydrate arm (N=51) of their RCT, 3.55 ± 0.63 kg, than in the low-fat arm (N=51) which showed a mean reduction of 0.92 ± 0.40 kg ($p=0.001$). **Level 1+**

The same RCT reported that glycaemic control improved in both arms of the trial. Improvements were greater in the low-carbohydrate arm, HbA_{1c} decreased from a baseline of $9.00 \pm 0.20\%$, by $0.55 \pm 0.17\%$, but this did not reach statistical significance. In the low-fat arm HbA_{1c} decreased from a baseline of $9.11 \pm 0.17\%$ by $0.23 \pm 0.13\%$ ($p=0.132$). **Level 1+**

Studies comparing low- or modified-fat diets with reduced calorie diets

Barnard et al.¹⁴ investigated the effects of a low-fat vegan diet compared with a diet based on ADA guidelines, on body weight and glycaemic control in an RCT with 99 Type 2 diabetics, followed up for 22 weeks. During the study period, 43% (21/49) of vegan participants and 26% (13/50) of ADA participants reduced their diabetic medications, mainly as a result of hypoglycaemia. Eight per cent in each group, 4/49 of the vegan group and 4/50 of the ADA group, increased their medications.

The study concluded that for the whole sample, body weight was reduced in both groups by 5.8 kg in the vegan group and 4.3 kg in the ADA group, but this difference was not statistically significant ($p=0.082$). In those whose medication was stable this difference was significant with a 6.5 kg reduction in the vegan group, and 3.1 kg in the ADA group, $p<0.001$. BMI declined by 2.1 ± 1.5 kg/m² in the vegan group and by 1.5 ± 1.5 kg/m² in the ADA group ($p=0.08$). The waist-to-hip ratio declined in the vegan group 0.02 ± 0.01 but not in the ADA group ($p=0.003$). Level 1+

With respect to glycaemic control, the RCT stated that while the HbA_{1c} decline in both groups was statistically significant from their baseline values with a decline of 0.96% ($p<0.0001$) in the vegan group and 0.56% ($p=0.0009$) in the ADA group, there was no significant difference between the groups ($p=0.089$). Again the results were different in those participants whose medication was unchanged. The HbA_{1c} decline was greater in the vegan group, $1.23\pm 1.38\%$, than in the ADA group, $0.38\pm 1.11\%$, ($p=0.01$). Level 1+

Table 6.1 Summarised results for body weight reduction and glycaemic control across RCTs

RCTs	T=	Comparison	Comparison	Weight/BMI	Glycaemic control
Li (2005) ¹³	1 year	Soy-based meal replacement	Individualised diet	Weight and BMI=NS	HbA _{1c} significantly lower in meal replacement arm
Redmon (2003) ¹⁷	1 year	Sibutramine + low-calorie diet + meal replacement	Individualised diet	Weight reduction significantly higher in combination arm	HbA _{1c} significantly lower in combination arm*
Daly (2006) ¹⁶	3 months	Low-carbohydrate diet	Reduced portion low-fat diet	Weight reduction significantly higher in carbohydrate arm	HbA _{1c} =NS
Barnard (2006) ¹⁴	22 weeks	Low-fat vegan diet	Diet based on ADA guidelines	Weight=NS	HbA _{1c} =NS

* A 5 kg decrease in weight at 1 year was associated with a 0.4% decrease in HbA_{1c}.

Observational studies

In an observational study with 4 years of follow-up,²⁰ the authors investigated the association between eating behaviour and long-term weight gain. Ninety-seven Type 2 diabetics were recruited at diagnosis and after initial nutrition advice were followed up for a period of 4 years.

The study found that at the end of follow-up, mean body weight change in men was a gain of 1.3 ± 5.4 kg, whereas in women, there was a mean body weight reduction of -1.1 ± 5.0 kg. These changes were not statistically significant, (p values not given). Similarly, BMI increased in men by 0.42 ± 1.76 kg/m² and decreased in women by 0.40 ± 1.89 kg/m², (p values not given). Glycaemic outcomes were not reported. Level 2+

In the second observational study,¹⁹ weight loss over the 6.5-year follow-up is not reported. However, metabolic control did improve in patients over the period, with the proportion of patients with HbA_{1c} <7% increasing from 52.4% to 64.3% in men and from 43.9 to 50.9% in women. It was not reported whether or not this was significant. **Level 3**

▷ Blood pressure and blood lipid control outcomes

RCTs

Studies that compared a meal replacement intervention with a reduced calorie diet

The RCT by Li et al.,¹³ reporting on the comparison of a soy-based meal replacement plan with an individualised diet plan, did not report on changes in blood pressure during the study.

For the blood lipid control outcomes, while there were no significant differences between groups during the study for lipid parameters, there were differences within the groups when compared to baseline values. In the meal replacement group, there were decreases in total cholesterol, triglycerol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) at the end of the study, however these changes were only significant in the triglycerol group with an overall decrease from baseline of 28.00 mg/dl (p=0.038). Decreases in total cholesterol were significant at 3 (p<0.0001) and 6 (p=0.0037) months, but at 12 months with a reduction of 10.76 mg/dl from baseline, this was not significant (p=0.084). LDL decreased by 11.04 mg/dl at 3 months (p=0.024), but at 12 months the change from baseline had reduced to 6.10 mg/dl (p=0.255). HDL had decreased by 0.97 mg/dl at 12 months (p=0.345). In the individualised diet plan group, after initial decreases at 3 or 6 months, at 12 months there were increases in total cholesterol by 5.26 mg/dl (p=0.396), LDL by 8.76 mg/dl (p=0.129) and HDL by 2.26 mg/dl (p=0.012). Only in triglycerol levels was there a sustained decrease at 12 months with a reduction from baseline of 28.89 mg/dl (p=0.119). **Level 1+**

In the study by Redmon¹⁷ which compared a combined intervention (described above) with an individualised diet plan, at 1 year there were reductions in systolic and diastolic blood pressure in both groups, although this did not differ between the groups. Systolic blood pressure reduced in the combination group by 6±3 mmHg and by 6±2 mmHg in the comparison group. Diastolic blood pressure reduced in the combination group by 3±1 mmHg and by 6±2 mmHg in the comparison group. **Level 1+**

At 1 year, changes in fasting cholesterol, HDL, LDL and fasting triglycerides did not differ between groups. There were reductions from baseline values in fasting cholesterol and LDL cholesterol in both groups, with a decrease in fasting cholesterol of 6±8 mg/dl in the combination therapy group and 17±9 mg/dl in the comparison group (p=0.90). LDL decreased by 12±5 mg/dl in the combination therapy group and 13±6 mg/dl in the comparison group (p=0.89). Fasting triglycerides decreased by 46±24 mg/dl in the combination group compared to an increase of 8±18 mg/dl in the comparison group, however this was not significant (p=0.07). **Level 1+**

Studies comparing a low-carbohydrate with a low-fat diet

At 12 weeks of follow-up, in the low-carbohydrate arm of this RCT¹⁶ there was a reduction in systolic blood pressure of 6.24±2.96 mmHg and a reduction of 0.39±2.64 mmHg in the low-fat arm, with no significant difference between the arms (p=0.147). **Level 1+**

With respect to lipid parameters, there was a greater reduction in the total cholesterol: HDL ratio in the low-carbohydrate arm, mean reduction of 0.48, than in the low-fat arm, mean reduction 0.10 ($p=0.011$). There were also reductions in triglycerides in both arms, 0.67 mmol/l in the low-carbohydrate arm and 0.25 in the low-fat arm, which did not approach statistical significance ($p=0.223$). Level 1+

Studies comparing low- or modified-fat diets with reduced calorie diets

In the RCT comparing the low-fat vegan diet with the ADA diet,^{14,20} there were non-significant reductions in systolic and diastolic blood pressure in both groups. In the vegan group systolic blood pressure decreased by 3.8 ± 12.6 mmHg ($p<0.05$) compared with baseline and in the ADA group by 3.6 ± 13.7 mmHg from baseline, with no significant difference between the groups ($p=0.93$). Similarly the reduction in diastolic blood pressure was greater in the vegan group, 5.1 ± 8.3 mmHg ($p<0.0001$) than in the ADA group 3.3 ± 8.8 mmHg ($p<0.05$) although this was not different between groups ($p=0.30$). Level 1+

For the entire sample, although lipid parameters decreased significantly from baseline values, there were no significant differences between groups. Among those whose lipid controlling medications remained constant (vegan $N=39/49$; ADA $N=41/50$), total cholesterol reduced in the vegan groups by 33.5 ± 21.5 mg/dl ($p<0.0001$), in the ADA group by 19.0 ± 28.5 mg/dl ($p<0.0001$) and this was a significantly different between groups ($p=0.01$). Reductions in HDL cholesterol were not significantly different between the groups.

Reductions in non-HDL cholesterol were significantly lower than baseline in the vegan groups 27.6 ± 21.1 mg/dl ($p<0.0001$) and in the ADA group 16.3 ± 30.1 mg/dl ($p<0.05$), but not significantly different between the groups ($p=0.05$).

LDL cholesterol reduced in the vegan group by 22.6 ± 22.0 mg/dl ($p<0.0001$) and in the ADA group by 10.7 ± 23.3 mg/dl ($p<0.05$), and was significantly different between the groups ($p=0.02$). The total-to-HDL cholesterol ratio and triglyceride concentrations fell for both groups, but there was no difference between the groups. Level 1+

Table 6.2 Summarised results for blood pressure and lipid levels across RCTs

RCTs	T=	Comparison	Comparison	Blood pressure	Lipid levels
Li (2005) ¹³	1 year	Soy-based meal replacement	Individualised diet	No changes	NS differences
Redmon (2003) ¹⁷	1 year	Sibutramine + low calorie diet + meal replacement	Individualised diet	NS differences	NS differences
Daly (2006) ¹⁶	3 months	Low-carbohydrate diet	Reduced portion low-fat diet	NS differences	TC:HDL ratio significantly lower in carbohydrate arm
Barnard (2006) ¹⁴	22 weeks	Low-fat vegan diet	Diet based on ADA guidelines	NS differences	NS differences

Observational studies

In the observational study investigating the effect of eating behaviours on weight,²⁰ changes in blood pressure or lipid profiles were not reported.

In the diabetes nutrition and complications trial¹⁹ changes in blood pressure were reported as the proportion of patients who had a systolic blood pressure <130 mmHg, which decreased from 28.6% at baseline to 11.9% at the end of the study. Similarly in women there was a decrease from 15.8% at baseline to 8.8% after 6.5 years. The proportion of patients with a diastolic blood pressure of <80 mmHg decreased from 26.2% to 21.4% and from 31.6% to 28.1% in men and women respectively.

In this study they reported the number of patients who were adherent to the ADA diet recommendations and were able to achieve the recommended intakes of various types of fats. They found that levels of adherence to the recommendations was low with only 26.6% of patients consuming the recommended amount of saturated fatty acids (SFAs), 13.0% consuming the recommended $\geq 10\%$ of dietary energy from polyunsaturated fats, and 38.5% consuming the recommended $\geq 60\%$ of dietary energy from carbohydrates and monounsaturated fats. They also estimated that 46.4% of patients consumed a ratio of polyunsaturated fatty acids (PUFAs)/SFAs >0.4 and 69% consumed a ratio of monounsaturated fats (MUFAs)/SFAs >1.5. Patients who consumed MUFAs/SFAs <1.5 had a 3.6–4.7 times greater risk of developing diabetic complications (confidence intervals (CIs) not presented). Patients who consumed PUFAs/SFAs <0.4 were 3.4–8.2 times more at risk of developing diabetic complications. Level 3

6.1.5 From evidence to recommendations

The GDG noted that there was little new evidence to warrant any change to previous views in this field. The major consensus-based recommendations from the UK and USA emphasise sensible practical implementation of nutritional advice for people with Type 2 diabetes. Other relevant NICE guidance should be considered where relevant, including clinical guideline no. 43 on the assessment and management of overweight and obesity in adults and children and clinical guideline no. 48 which gives dietary and lifestyle advice post-MI. Overlap with the NICE/RCP Type 1 diabetes guideline was noted. Management otherwise will concentrate on principles of healthy eating (essentially those for optimal cardiovascular risk protection), and reduction of high levels of free carbohydrate in food that are hyperglycaemic in the presence of defective insulin secretory reserve.

If people are currently gaining weight, weight maintenance is advantageous.

The GDG noted that in some people with Type 2 diabetes and weight problems it might be appropriate to consider pharmacotherapy, however this was not within the clinical questions addressed.

As with Patient Education (see chapter 5) delivery of dietary advice was noted to depend not only on specific skills, but also required all members of the diabetes care team to be familiar with local policy and thus delivering consistent advice.

Concerns continue to be noted over the promotion of 'diabetic foods' which may be low in classical sugars but high in calories and thus unsuitable as well as unnecessary for the overweight. While reduction in weight was clearly understood to be beneficial through improvements in

insulin insensitivity (whether relying on endogenous or exogenous insulin), low-carbohydrate diets were noted to be of unproven safety in the long term and thus could not be endorsed. Similarly high-protein diets are acknowledged as promoting short-term weight loss, but cannot be recommend as safe in the long term.

A dietary plan for people with diabetes would follow the principles of healthy eating in the population, and thus include carbohydrate from fruits, vegetables, wholegrains, and pulses (and thus high fibre and low glycaemic index), reduction in salt intake, the inclusion of low-fat milk and oily fish, and control of saturated and trans fatty acid intake.

The importance of advice on alcohol to the overweight and to those prone to hypoglycaemia through use of insulin secretagogues or insulin was judged important.

RECOMMENDATIONS

- R7 Provide individualised and ongoing nutritional advice from a healthcare professional with specific expertise and competencies in nutrition.
- R8 Provide dietary advice in a form sensitive to the individual's needs, culture and beliefs being sensitive to their willingness to change, and the effects on their quality of life.
- R9 Emphasise advice on healthy balanced eating that is applicable to the general population when providing advice to people with Type 2 diabetes. Encourage high-fibre, low glycaemic index sources of carbohydrate in the diet, such as fruit, vegetables, wholegrains and pulses; include low-fat dairy products and oily fish; and control the intake of foods containing saturated and trans fatty acids.
- R10 Integrate dietary advice with a personalised diabetes management plan, including other aspects of lifestyle modification, such as increasing physical activity and losing weight.
- R11 Target, for people who are overweight, an initial body weight loss of 5–10%, while remembering that lesser degrees of weight loss may still be of benefit and that larger degrees of weight loss in the longer term will have advantageous metabolic impact.
- R12 Individualise recommendations for carbohydrate and alcohol intake, and meal patterns. Reducing the risk of hypoglycaemia should be a particular aim for a person using insulin or an insulin secretagogue.
- R13 Advise individuals that limited substitution of sucrose-containing foods for other carbohydrate in the meal plan is allowable, but that care should be taken to avoid excess energy intake.
- R14 Discourage the use of foods marketed specifically for people with diabetes.
- R15 When patients are admitted to hospital as inpatients or to any other institutions, implement a meal planning system that provides consistency in the carbohydrate content of meals and snacks.

6.2 Management of depression

6.2.1 Clinical introduction

Psychological well-being is clearly part of being healthy. It is an important part of healthcare management of any condition where psychological health is impaired or where it has particular impact on clinical management.

There is evidence of a high prevalence of psychological ill-health in people with diabetes, notably for depression,²¹ which is often under-recognised.²² Additionally because of the importance of self-care to the management of the condition, there is evidence that psychological ill-health is associated with adverse effects on other aspects of the long-term health of people with Type 2 diabetes.^{23–25}

Formal assessment of psychological well-being is not a standard part of practice in diabetes care in the UK. Other guidelines, including the NICE guideline for people with Type 1 diabetes, have emphasised the importance of recognising and managing depression. Only general recommendations have been made regarding being alert to problems, availability of skills to manage routine psychological disorders, and of appropriate referral to those with special expertise where the condition is more severe.²⁶ NICE has recently published a guideline on the management of depression.²⁷

No evidence search has been performed for the purpose of the current guideline due to the availability of the NICE depression guideline. People with Type 2 diabetes with psychological and/or depressive disorders should be identified by continuing professional awareness, and managed in accordance with current national guidelines.

7 Glucose control levels

7.1 Clinical monitoring of blood glucose control

7.1.1 Clinical introduction

The risk of arterial disease and microvascular complications in people with diabetes are known to be related to the extent of hyperglycaemia with time. While the lifestyle, oral agent, and injectable therapies discussed in this guideline can improve blood glucose control, their efficacy is limited, as the underlying pathogenesis of diabetes worsens with time. As symptoms are not a reliable guide to blood glucose control in people on therapy, it is important to have an accurate means of measuring blood glucose control over time, to enable decision-making.

This section addresses the clinical questions as to the tests of blood glucose control best predictive of future vascular damage from diabetes, the nature of the relationship between test results and such vascular risk, how tests should be deployed in clinical practice, and how they might be interpreted.

7.1.2 Methodological introduction

The UKPDS is a large (N=3,867) landmark study with a 10-year follow-up period. It evaluated whether in people newly diagnosed with Type 2 diabetes more intense therapy to achieve tighter glycaemic control would result in a greater reduction in the incidence of microvascular and macrovascular complications than would conservative therapy. Due to the size and duration of this study, other studies published from 2001 onwards in this area were only considered if they had a sample size of at least N=2,000 people with Type 2 diabetes, or mixed Type 1 and 2 diabetes populations. Studies were not reviewed if they simply found significant associations between HbA_{1c} and diabetes complications without giving further information about that association.

Published results from the UKPDS were included in this review if they specifically reported results on the relationship between HbA_{1c} and microvascular and/or macrovascular complications. One prospective observational study²⁸ was identified which analysed the UKPDS glucose control results in terms of both macrovascular and microvascular complications.

A meta-analysis²⁹ was also identified which assessed the association between glycosylated haemoglobin and cardiovascular (CV) disease in people with diabetes. This included an analysis of 10 studies specifically of people with Type 2 diabetes. As some of the cohorts included in this analysis were participants in the UKPDS study, it is necessary to be alert to double-counting.

Other observational studies identified, which were not published results of the UKPDS study or included in the meta-analysis, considered the relationship between glycaemic control and CV and renal risk,³⁰ and between glycaemic control and heart failure.³¹

7.1.3 Health economic methodological introduction

One paper was identified which was excluded from further consideration as it was not possible to compare the costs between patients with good or poor control because the well-controlled patients were probably earlier in the course of the disease.³² Two evaluations based on the UKPDS were identified that were considered to be of good quality.³³

7.1.4 Evidence statements

- The risk of each of the microvascular and macrovascular complications of Type 2 diabetes and cataract extraction was strongly associated with hyperglycaemia as measured by updated mean HbA_{1c}.
- There was no indication of a threshold for any complication below which risk no longer decreased, nor a level above which risk no longer increased.

Table 7.1 UKPDS study²⁸

N=3,642 included in the analysis of relative risk

Level of evidence 2++

Microvascular/macrovascular complications or mortality	1% reduction in updated mean HbA_{1c} was associated with reductions in risk of*
Any endpoint related to diabetes (MI, sudden death, angina, stroke, renal failure, lower extremity amputation or death from peripheral vascular disease, death from hyperglycaemia or hypoglycaemia, heart failure, vitreous haemorrhage, retinal photocoagulation, and cataract extraction)	21%, 95% CI 17% to 24% (p<0.0001)
For deaths related to diabetes (MI, sudden death, stroke, lower extremity amputation or fatal peripheral vascular disease, renal disease, hyperglycaemia or hypoglycaemia)	21%, 95% CI 15% to 27% (p<0.0001)
All cause mortality	14%, 95% CI 9% to 19% (p<0.0001)
MI (fatal MI, non-fatal MI, and sudden death)	14%, 95% CI 8% to 21% (p<0.0001)
Stroke (fatal and non-fatal stroke)	12%, 95% CI 1% to 21% (p=0.035)
Peripheral vascular disease (lower extremity amputation or death from peripheral vascular disease)	43%, 95% CI 31% to 53% (p<0.0001)
Microvascular complications (retinopathy requiring photocoagulation, vitreous haemorrhage, and fatal or non-fatal renal failure)	37%, 95% CI 33% to 41% (p<0.0001)
Heart failure (non-fatal, without a precipitating MI)	16%, 95% CI 3% to 26% (p=0.016)
Cataract extraction	19%, 95% CI 11% to 26% (p<0.0001)
The adjusted incidence rates for any endpoint related to diabetes increased with each higher category of updated mean HbA _{1c} , with no evidence of a threshold and with a three-fold increase over the range of updated mean HbA _{1c} of less than 6%, to equal to, or more than, 10%.	
* Data adjusted for age at diagnosis of diabetes, sex, ethnic group, smoking, presence of albuminuria, systolic blood pressure, high and low density lipoprotein cholesterol and triglycerides	

- There was an increase in CV risk with increasing levels of glycosylated haemoglobin in persons with Type 2 diabetes.

Table 7.2 Meta-analysis of prospective cohort studies²⁹

N=10 studies in people with Type 2 diabetes

Level of evidence 2+

Cardiovascular complications or mortality	Pooled RR for each 1 percentage point increase in glycosylated haemoglobin*
Total CV (combining 10 studies of coronary heart disease alone, stroke alone, and stroke and coronary heart disease combined)	1.18 (95% CI 1.10 to 1.26)
Coronary heart disease (combining five studies of MI, angina and IHD)	1.13 (95% CI 1.06 to 1.20)
Fatal coronary heart disease (combining five studies of fatal MI, angina and IHD)	1.16 (95% CI 1.07 to 1.26)
Cerebrovascular disease (combining three studies of fatal and non-fatal stroke)	1.17 (95% CI 1.09 to 1.25)
Peripheral arterial disease (combining three studies of lower extremity peripheral arterial disease, amputation and claudication)	1.28 (95% CI 1.18 to 1.39)

* All RR estimates in the pooled analyses were from the most fully adjusted multivariate model
IHD, ischaemic heart disease; RR, relative risk

- There was an independent progressive relationship between GHb and incident cardiovascular events, renal disease and death.

Table 7.3 Prospective observational study of participants in the Heart Outcomes Prevention Evaluation (HOPE) study³⁰

N=3,529

Level of evidence 2+

Cardiovascular and renal complications	A 1% absolute rise in updated glycated haemoglobin was associated with relative risks of*
Future CV events (the first occurrence of one or more of the following: non-fatal MI, stroke or CV death)	1.07, 95% CI 1.01 to 1.13 (p=0.014)
Death	1.12, 95% CI 1.05 to 1.19 (p=0.0004)
Hospitalisation for heart failure	1.20, 95% CI 1.08 to 1.33 (p=0.0008)
Overt nephropathy	1.26, 95% CI 1.17 to 1.36 (p=0.0001)

There was a consistent and progressive relationship between the GHb level (both baseline and updated) and the age and sex adjusted relative hazard of the above outcomes. All showed significant trends with the strongest relationships being seen with the updated GHb level

* After adjusting for age, sex, diabetes duration, blood pressure, BMI, hyperlipidaemia and ramipril

- There was an independent graded association between glycaemic control and incidence of hospitalisation and/or death due to heart failure.

Table 7.4 Observational study of participants on the Kaiser Permanente Medical Care Program of Northern California diabetes registry³¹

N=48,858

Level of evidence 2+

Cardiovascular complications	The relative risk associated with a 1% increase in HbA_{1c}*
Composite of hospitalisation for heart failure or death with heart failure as the underlying cause	1.08, 95% CI 1.05 to 1.12
A concentration of HbA _{1c} more than or equal to 10% relative to HbA _{1c} less than 7%, was associated with a 1.6 fold increased heart failure risk (for hospitalisation or death)	
* This model was adjusted for age, sex, ethnicity, education level, smoking, alcohol consumption, self-reported hypertension, obesity, cardioprotective medicine used at baseline, type of diabetes and treatment, duration of diabetes and incidence of MI during follow-up	

7.1.5 Health economic evidence statements

The UKPDS included an analysis of intensive blood glucose control with metformin for overweight patients compared to conventional treatment primarily with diet. The study included 753 overweight (>120% ideal body weight) patients with newly diagnosed Type 2 diabetes from 15 hospital-based clinics in England, Scotland and Northern Ireland. Of these patients 342 were allocated to an intensive blood glucose control policy with metformin and 411 were allocated to conventional treatment, primarily with diet alone. The study was conducted from 1977 to 1991. The median follow-up period was 10.4 years.

In the conventional policy group the glycaemic goal was to obtain the lowest fasting plasma glucose (FPG) attainable with diet alone. In the intensive policy group the aim was a FPG of less than 6.0 mmol/l by increasing the dose of metformin from 500 to 2,550 mg a day as required. Use of metformin for intensive blood glucose control in overweight patients was found to confer a 32% risk reduction for any diabetes related endpoint and a 42% risk reduction for diabetes related deaths compared with a conventional policy.

In the 2001 cost-effectiveness analysis, intensive treatment with metformin cost on average £258 less than conventional treatment, and resulted in a longer life expectancy of 0.4 years.³⁴

In the 2005 cost-utility analysis the discounted cost (6% discount rate) of an intensive blood glucose control policy with insulin or sulphonylureas was on average £884 more per patient and the discounted benefits gained were 0.15 quality of life-adjusted year (QALY), a cost per QALY gained of £6,028.³³

The discounted cost of intensive blood glucose control policy with metformin in overweight patients was on average £1,021 less than the conventional policy and had a longer discounted life expectancy of 0.55 QALYs, making this intensive treatment strategy both cost-saving and more effective.³⁴

7.1.6 From evidence to recommendations

There were a number of difficulties agreeing the level at which therapeutic interventions should begin or be enhanced. It was agreed that people with diabetes and the professionals advising

them needed a reference level if optimum glucose control is to be obtained. It was noted that treat-to-target studies achieved much better outcomes than studies with less well defined aims.

The evidence base has not significantly moved on since the earlier guideline, except to support the conclusions of the UKPDS epidemiological analysis (that CV risk fell linearly well into the normal range of HbA_{1c}). A single target figure is unhelpful as this may vary in individuals depending on the:

- quality of life that might have to be sacrificed in reaching the target
- extent of side effects
- resources available for management.

An individual requiring insulin for adequate control, who is at risk and prone to hypoglycaemia would have a higher personal target of glucose control than someone newly diagnosed who had adopted significant lifestyle changes.

Microvascular risk data suggests higher glucose control targets. This led to a stronger recommendation in the NICE/RCP Type 1 diabetes guideline for those at no added macrovascular disease risk. Most of those with Type 2 diabetes can be regarded as at high macrovascular risk, by reason of phenotype or age.

Cardiovascular risk can be reduced by 10–15% per 1.0 % reduction of HbA_{1c}, the treatment effect and epidemiological analysis of UKPDS giving the same conclusions. Mean levels of close to 6.5 % were achieved in the first 5 years of the UKPDS in both the main glucose study and the obese ('metformin') study in the active treatment arms. The epidemiological analysis supports a linear fall in macrovascular risk down to 6.0 % or below, and this will largely reflect data from the more actively managed group.

However, expensive therapies or very intensive interventions are required to achieve glucose control in the normal range in most people with diabetes. Consequently a population target should not be any tighter than the HbA_{1c} of 6.5 % previously chosen for those at macrovascular risk. Nearly all people with Type 2 diabetes are of high CV risk, usually in association with insulin insensitivity, but if not with age. Additionally there has been very recent concern (no evidence yet to review) about pursuing very intensive glucose control (target <6.0 %) in people with higher CV risk and longer duration of diabetes, mostly on multiple insulin injection therapy.³⁵

The GDG were made aware of the issue of postprandial plasma glucose control, and that it could be specifically targeted in some circumstances and with some interventions. A review of the literature in this regard had not been performed for the present guideline. However, the GDG were informed that an evidence-based guideline had been published by the IDF since completion of the current guideline draft, and that no RCTs addressing the question with true health outcomes as an endpoint had been identified. Accordingly a view to treat this aspect specifically relied on weaker evidence. Accordingly the GDG were content only to make recommendations on the identification of pre-meal and postprandial hyperglycaemia, and levels for intervention.

The GDG expressed concern that intervention levels for enhancement of therapy should not be confused with audit or reimbursement standards. These types of standards are set with much greater attention being paid to attainability.

RECOMMENDATIONS

- R16** When setting a target glycated haemoglobin HbA_{1c}:
- involve the person in decisions about their individual HbA_{1c} target level, which may be above that of 6.5 % set for people with Type 2 diabetes in general
 - encourage the person to maintain their individual target unless the resulting side effects (including hypoglycaemia) or their efforts to achieve this impair their quality of life
 - offer therapy (lifestyle and medication) to help achieve and maintain the HbA_{1c} target level
 - inform a person with a higher HbA_{1c} that any reduction in HbA_{1c} towards the agreed target is advantageous to future health
 - avoid pursuing highly intensive management to levels of less than 6.5 %.
- R17** Measure the individual's HbA_{1c} levels at:
- 2–6-monthly intervals (tailored to individual needs), until the blood glucose level is stable on unchanging therapy; use a measurement made at an interval of less than 3 months as an indicator of direction of change, rather than as a new steady state
 - 6-monthly intervals once the blood glucose level and blood glucose lowering therapy are stable.
- R18** If HbA_{1c} levels remain above target levels, but pre-meal self-monitoring levels remain well controlled (<7.0 mmol/l), consider self-monitoring to detect postprandial hyperglycaemia (>8.5 mmol/l), and manage to below this level if detected (see chapters 9–11).
- R19** Measure HbA_{1c} using high-precision methods and report results in units aligned with those used in DCCT Trial (or as recommended by national agreement after publication of this guideline).²¹⁸
- R20** When HbA_{1c} monitoring is invalid (because of disturbed erythrocyte turnover or abnormal haemoglobin type), estimate trends in blood glucose control using one of the following:
- fructosamine estimation
 - quality-controlled plasma glucose profiles
 - total glycated haemoglobin estimation (if abnormal haemoglobins).
- R21** Investigate unexplained discrepancies between HbA_{1c} and other glucose measurements. Seek advice from a team with specialist expertise in diabetes or clinical biochemistry.

8 Self-monitoring of plasma glucose

8.1.1 Clinical introduction

Self-monitoring is the only direct method by which a person with diabetes can be aware of their level of control of blood glucose. It has utility when used with therapies of erratic effect, those requiring considerable dose adjustment (notably insulin), and in those whose therapies put them at risk of hypoglycaemia. More controversial, except for people using insulin, is the use of self-monitoring to provide feedback on the impact of lifestyle measures on blood glucose control, and as part of the overall educational package designed to enhance self-care. Indirect monitoring using urine glucose tests is cheaper, but also delivers less information than plasma glucose monitoring.

This section addresses the clinical question of the role of self-monitoring of plasma glucose in people at different stages of the condition and on different therapies, and its integration with other key processes of care such as patient education.

8.1.2 Methodological introduction

Three recent systematic reviews^{36–38} were identified which compared self-monitoring of blood glucose (SMBG) with usual care and/or with self-monitoring of urine glucose (SMUG) in patients with Type 2 diabetes not using insulin. One was a Cochrane review³⁸ of six RCTs without a meta-analysis. The same authors also published a second review³⁷ with the same studies including a meta-analysis. The third review was a meta-analysis of eight RCTs.³⁶ Although all of these reviews were of high methodological quality, this was not true of the studies included within them. In two reviews,^{37,38} four out of six studies were found to be of low quality and in the other review,³⁶ five of the eight studies were judged to be of moderate risk of bias and three to be of high risk of bias. A further systematic review and meta-analysis included Type 2 diabetic patients that were on insulin treatment and used Bayesian methods to conduct a mixed treatment comparison.³⁹

It should be noted that the two Cochrane reviews published by the same authors^{37,38} did not perform a meta-analysis because they considered the studies they had identified to have ‘clinical heterogeneity’, in terms of baseline data of the patients and type of interventions between the studies. With regard to the interventions, the authors concluded that there were also discrepancies in monitoring frequency, training the patient in terms of the technique and educating the patient on how the data should be acted upon.

The meta-analysis by Jansen³⁹ scored the included studies for internal validity and adjusted for this in sensitivity analysis. This was also the only new study that compared the effects of urine versus blood self-monitoring on glycaemic control, albeit in an indirect comparison.

A protocol for a new 4-year UK trial in this area (the Diabetes Glycaemic Education and Monitoring (DiGEM) trial)⁴⁰ was identified and the results of this, once available, should clarify if and how to use SMBG, as part of a self-management programme. In one arm, a self-monitoring group will receive support in interpreting and applying the results of blood testing to enhance motivation and maintain adherence to diet, physical activity and medication regimens.

Two RCTs were identified which compared SMBG with no monitoring.^{41,42} One study did not include insulin-treated patients.⁴² The other included patients treated with insulin and the use of blood glucose monitoring in one arm of the study.⁴¹

Four cohort studies were also identified.^{43–46} As noted in the previous guideline, it can be argued that limited credence can be given to observational study associations between blood glucose control and self-monitoring as those patients and healthcare professionals who advocate self-monitoring may be the same people who are motivated to achieve better control.

One cross-sectional study⁴⁷ and one case-series⁴⁸ were also identified.

The GDG requested for a separate qualitative search to be conducted on this topic. This search identified two papers which considered self-monitoring from a patient perspective.^{49,50} The papers reported results from the same qualitative Scottish study although the papers had slightly different aims. One explored the respective merits of urine testing and SMBG from the perspective of newly diagnosed patients with Type 2 diabetes⁴⁹ whilst the other explored the pros and cons of self-blood glucose monitoring from the patients' perspective.⁵⁰

8.1.3 Health economic methodological introduction

One cost-effectiveness analysis was identified in the search.⁵¹ It did not include enough detail on the costs and utilities to adequately interpret the results.

A cost analysis of implementing intensive control of blood glucose concentration in England identified increased frequency of home glucose tests as a main contributor to the total costs of intensive control.⁵² It was estimated that the additional management costs of implementing intensive control policies would be £132 million per year, of which £42.2 million would be on home glucose tests. The sensitivity analysis results found that changes in the unit cost of home blood glucose strips (baseline cost £0.27, range tested £0.16–£0.40) in the proportion of patients already being managed intensively, and the costs of intensifying management, had the largest impact on the cost of implementation.

8.1.4 Evidence statements

(See the methodological introduction for commentary on systematic reviews of RCTs.)

Even though the Cochrane reviews^{37,38} were not able to meta-analyse the data (due to clinical and methodological heterogeneity) the authors concluded that SMBG might be effective in improving glycaemic control in patients with Type 2 diabetes who are not using insulin. Authors also stated that a well designed large RCT assessing the benefits (including patient-related outcomes) of SMBG alongside patient education is required. **Level 1+**

The other review³⁶ concluded that, 'in the short term, and when integrated with educational advice, self-monitoring of blood glucose as an adjunct to standard therapy, may contribute to improving glycaemic control among non-insulin requiring Type 2 diabetes patients'. **Level 1+**

In an indirect analysis, Jansen³⁹ found a non-significant reduction in HbA_{1c} of 0.3% when interventions with SMBG were compared with those associated with SMUG.

The study by Jansen also reported that interventions with SMBG were found to be more effective in reducing HbA_{1c} than interventions without self-monitoring. The reduction in HbA_{1c} was statistically significant and it was estimated to be around 0.4%. This effect was increased when regular feedback was added to the SMBG and was shown in both an insulin-treated Type 2 diabetes group, and in a group of Type 2 diabetes patients that included those being treated with oral agents. **Level 1+**

An RCT looking at the effects of an education manual⁴¹ on blood glucose monitoring found that the greatest reduction in HbA_{1c} occurred in the education manual group ($-0.13 \pm 1.28\%$) compared with both the SMBG ($-0.04 \pm 1.31\%$) and standard care ($0.04 \pm 1.10\%$) groups. The authors did not report whether there was a significant difference between groups. **Level 1+**

A second multicentre RCT⁴² found a significantly greater reduction in HbA_{1c} in the SMBG compared to the non-SMBG group ($p=0.0086$). **Level 1+**

A retrospective cohort study performed in the USA ($N=976$) found that duration of SMBG (0–3 years) was not a significant predictor of HbA_{1c} values in those with Type 2 diabetes on oral medication.⁴⁵ **Level 2+**

In a German retrospective cohort study of 1,609 patients with Type 2 diabetes, hazard ratios indicated that SMBG was associated with a 32% reduction in morbidity for combined macrovascular (MI and stroke) and microvascular (foot amputation, blindness or end-stage renal failure) non-fatal endpoints ($HR=0.68$, 95% CI 0.51–0.91, $p=0.009$). This was despite an increase of microvascular events, and a 51% reduction in mortality over the observation period ($HR=0.49$, 95% CI 0.31–0.78, $p=0.003$) where mean follow-up was 6.5 years. In those not receiving insulin, SMBG was associated with a 28% reduction in combined non-fatal endpoints ($HR=0.72$, 95% CI 0.52–0.99, $p=0.0496$) and a 42% reduction in mortality over the observation period ($HR=0.58$, 95% CI 0.35–0.96, $p=0.035$).⁴⁴ **Level 2+**

A retrospective cohort study of people with diabetes in a US medical care programme⁴³ found greater SMBG practice frequency among new users, which was associated with a graded decrease in HbA_{1c} (relative to non-users) regardless of diabetes therapy ($p<0.001$). Changes in SMBG frequency among prevalent users were associated with an inverse graded change in HbA_{1c} but only among pharmacologically-treated patients ($p<0.0001$). **Level 2+**

A study including patients from the Fremantle Diabetes Study (FDS) cohort⁴⁶ over 5 years of follow-up did not find any difference in HbA_{1c} or in fasting plasma glucose, either overall or within treatment groups in patients who used SMBG than those who did not ($p \geq 0.05$). There were also no differences in HbA_{1c} or FPG between SMBG adherent and non-adherent users by treatment group ($p \geq 0.09$). **Level 2+**

In a qualitative study performed in Scotland of newly diagnosed Type 2 diabetics, 'patients reported strongly negative views of urine testing, particularly when they compared it with self-monitoring of blood glucose. Patients perceived urine testing as less convenient, hygienic and accurate than self-monitoring of blood glucose. Most patients assumed that blood glucose meters were given to those with a more advanced or serious form of diabetes. Patients often interpreted negative urine results as indicating that they did not have diabetes.'⁴⁹

A Scottish qualitative study sought newly diagnosed Type 2 diabetes patients' perspectives on the pros and cons of SMBG.

Pros of self-monitoring:

- provides a heightened awareness of, and evidence of, the condition
- when readings are within advised guidelines and fluctuations are easily interpretable, patients emphasise the positive role that monitoring has in their diabetes management. Low readings are a high point giving personal gratification
- cultivates independence from health services and enhances self-regulation.

Cons of self-monitoring:

- potentially, self-monitoring can raise anxiety about readings
- blood glucose parameters were found to be problematic by patients when they felt they were receiving contradictory information about upper thresholds or no guidance about ideal parameters
- lack of awareness as to how to manage hyperglycaemia
- increased self-responsibility accompanied by increased self-blame and negative emotional reactions to high glucose readings
- counter-intuitive readings could be sources of distress and anxiety, in some cases adversely effecting adherence to diabetic regimens by promoting nihilistic attitudes
- healthcare professionals were not interested in readings.⁵⁰

8.1.5 From evidence to recommendations

The newer meta-analyses did not add significantly to the views expressed in the previous Type 2 diabetes guideline. The findings of the ROSSO study⁴⁴ and the data from the large Kaiser Permanente cohorts⁴³ added considerable confidence to the view that SMBG was an integral part of effective patient education packages and enabled the effective use of many other therapies and lifestyle interventions. The view in the previous guideline that self-monitoring of plasma glucose is not a stand-alone intervention was endorsed.

Concern was expressed over a number of issues surrounding the successful use of self-monitoring, and recognised that its cost meant that it had to be effectively deployed. It should only be supported in the context of a provision of a package of care, including structured education, from a primary or secondary diabetes care team. The initial education should be provided by a properly trained and skilled professional with understanding of the problems of the technology. Also, the skills of people with diabetes in using the technology should be the subject of regular quality assurance (together with the devices) perhaps as part of the regular annual review process. Devices should be calibrated to plasma glucose levels in line with 2006 WHO recommendations.

The importance of self-monitoring to the effective use of insulin therapy and for those at risk of hypoglycaemia through leisure or work activities (including driving) on oral medications was noted. The frequency of monitoring that is useful to someone with diabetes is highly individual and it is inappropriate to put an artificial restriction on this. The usefulness of self-monitoring, is dependent on the ability of users and health professionals to interpret the data particularly in the early stages of use by a person with diabetes, implying proper education and professional training on these aspects.

Qualitative studies from Scotland suggested that people with diabetes disliked monitoring of urine glucose compared to the self-monitoring of plasma glucose, and did not find it useful.

Hyperglycaemic complications were related to exposure to high glucose levels in plasma, and there were no major studies like the ROSSO and Kaiser studies for urine glucose monitoring. The evidence that plasma glucose monitoring could be replaced by urine glucose monitoring was found to be poor.

Although the DiGEM study was published after the evidence cut-off date, it had been identified as potentially important on the basis of earlier information. However, at review the GDG felt that a study which viewed self-monitoring as a stand-alone intervention, and not as an element of a full educational programme, could not properly inform the appropriate use of self-monitoring. The GDG further noted that people who might already have benefited from self-monitoring were excluded from participation.

Adverse effects of self-glucose monitoring (inconvenience, finger pricking) limited the use and cost-effectiveness of the technology. Obsessional and psychological problems relating to use of self-monitoring were rare in real clinical practice.

RECOMMENDATIONS

- R22** Offer self-monitoring of plasma glucose to a person newly diagnosed with Type 2 diabetes only as an integral part of his or her self-management education. Discuss its purpose and agree how it should be interpreted and acted upon.
- R23** Self-monitoring of plasma glucose should be available:
- to those on insulin treatment
 - to those on oral glucose lowering medications to provide information on hypoglycaemia
 - to assess changes in glucose control resulting from medications and lifestyle changes
 - to monitor changes during intercurrent illness
 - to ensure safety during activities, including driving.
- R24** Assess at least annually and in a structured way:
- self-monitoring skills
 - the quality and appropriate frequency of testing
 - the use made of the results obtained
 - the impact on quality of life
 - the continued benefit
 - the equipment used.
- R25** If self-monitoring is appropriate but blood glucose monitoring is unacceptable to the individual, discuss the use of urine glucose monitoring.

9 Oral glucose control therapies (1): metformin, insulin secretagogues, and acarbose

9.1 Clinical introduction

Maintenance of glucose control to target levels is achieved in only very few people with Type 2 diabetes for more than a few months using lifestyle measures alone.^{53,54} Oral glucose-lowering drugs are then indicated, and the choice, order and combination in which these are used will reflect evidence of:

- prevention of microvascular and arterial damage
- control of blood glucose levels
- assessment of the inconvenience
- risks of side effects.

Glucose control deteriorates continually with time in most people with Type 2 diabetes – it is not a chronic stable condition.^{53,54} This is known to be due to progressive failure of insulin secretion.⁵⁵ Accordingly therapy has to be stepped up with time, one drug added to another until such time as only exogenous insulin replacement will suffice.

The evidence of efficacy and side effects differs between drug classes, and to a lesser extent between members of the same class. Since their introduction was over 40 years ago the cost of some generic drugs is low whilst newer drugs have inevitably incurred high development costs and are relatively expensive. Cost-effectiveness is then a relevant issue too. The parent guideline suggested the long established biguanides (metformin) and sulfonylureas as the usual choice of first- and second-line oral glucose-lowering therapy when indicated. These, and other insulin secretagogues working through the same mechanisms as sulfonylureas, are considered in this chapter, and the more expensive newer glucose-lowering drugs in the next chapter.

The clinical questions concern the order with which these oral glucose-lowering medications should be introduced and added to one another in different groups of people with Type 2 diabetes. Because such people vary in attributes (such as body weight) which can affect choice of medication, and because some medication side effects can have consequences for aspects of daily living (such as driving motor vehicles), blanket recommendations cannot be made for everyone with Type 2 diabetes.

9.2 Metformin

9.2.1 Methodological introduction

A large number of RCTs were identified in this area; included trials were limited to participants with Type 2 diabetes, a trial duration of at least 12 weeks and a sample size of 300 or more. Studies with smaller sample sizes were only included if there were no other larger studies for a particular comparison.

Two Cochrane reviews were identified.^{56,57} One considered the effectiveness of metformin monotherapy compared with placebo or any active combination.⁵⁶ The other review included studies of metformin alone or in combination with other treatments compared with placebo or a range of other treatments, with the aim of reporting deaths due to lactic acidosis and non-fatal cases of lactic acidosis.⁵⁷ Similarly, an RCT was identified which compared serious adverse events (AEs) and plasma lactate levels between metformin and non-metformin treated groups.⁵⁸

We identified a further five RCTs which compared metformin monotherapy with pioglitazone,⁵⁹ glimepiride,⁶⁰ metformin plus rosiglitazone,⁶¹ metformin and rosiglitazone as a fixed-dose combination,⁶² and metformin plus nateglinide.⁶³ Two of these studies had methodological limitations and were not considered further.^{60,61}

In one RCT, metformin and biphasic insulin was compared with biphasic insulin alone.⁶⁴

An additional RCT was identified and included which compared metformin immediate-release (MIR) with metformin extended-release (MXR).⁶⁵ The GDG subsequently felt that there might be relevant and important information in existence on the AE profile of these two formulations which had not been found during our search. Thus a focused call for evidence to all stakeholders was made. Following this, the GDG considered two RCTs (published in the same paper) which compared MXR against placebo,⁶⁶ and to a retrospective chart review comparing immediate-release and extended-release formulations.⁶⁷ Consideration was also given to four abstracts; however their usefulness is limited by the small number of patients included and the lack of detail inhibiting any assessment of study quality.⁶⁸⁻⁷¹

It should be noted that differing dosing and titration regimens and the differing populations included in all the studies, may limit direct comparison between studies.

9.2.2 Health economic methodological introduction

Five papers were identified in the literature search, of these three compared metformin monotherapy with metformin in combination and so were thought to be more appropriate evidence for other questions.⁷²⁻⁷⁴ One paper included a subgroup analysis of metformin monotherapy compared to nateglinide monotherapy, although the results of this analysis were not reported.⁷⁵ Two evaluations based on the UKPDS were identified that were considered to be of good quality.³³

9.2.3 Evidence statements

▷ Mortality and morbidity

In terms of mortality and morbidity, a Cochrane review⁵⁶ looked at the events listed in the Clinical Endpoint Analyses from the UKPDS* (UKPDS-34 1998). The systematic review found five studies providing data on mortality and/or morbidity outcomes (four RCTs in addition to the UKPDS).

In the UKPDS (median follow-up 10.7 years), among overweight (54% with obesity) participants allocated to intensive blood glucose control, metformin (N=342) showed a greater

* According to the Cochrane review, the UKPDS is the unique trial that has been specifically designed to determine whether tight glycaemia control decreases complications related to diabetes and increases life expectancy.

benefit than chlorpropamide, glibenclamide, or insulin (N=951) for any diabetes-related outcomes, and for all-cause mortality. For other outcomes including diabetes-related death, MI, stroke, peripheral vascular disease and microvascular, there were no significant differences between both comparison arms. **Level 1++**

In the same vein, the UKPDS found that overweight participants assigned to intensive blood glucose control with metformin (N=342) showed a greater benefit than overweight patients on conventional treatment (non-intensive blood glucose control, mainly with diet), (N=411), for any diabetes-related outcomes, diabetes-related death, all-cause mortality, and MI. For the rest of the outcomes such as stroke, peripheral vascular disease and microvascular, there were no significant differences between both comparison arms. **Level 1++**

After pooling data from the four non-UKPDS trials, the Cochrane review did not find significant differences among comparisons either for all-cause mortality or for ischemic heart disease (study durations ranged from 24 weeks to 2 years). **Level 1++**

Table 9.1 Metformin mortality and morbidity studies

Study/comparison	Outcome	Effect size (RR)
UKPDS: metformin vs sulfonylureas or insulin	Any diabetes-related outcomes	0.78 (95% CI 0.65 to 0.94) p=0.009
	All-cause mortality	0.73 (95% CI 0.55 to 0.97) p=0.03
	Diabetes-related death	NS
	Myocardial infarction	NS
	Stroke	NS
	Peripheral vascular disease	NS
	Microvascular	NS
UKPDS: metformin vs conventional (non-intensive blood glucose control, mainly with diet)	Any diabetes-related outcomes	0.74 (95% CI 0.60 to 0.90) p=0.004
	Diabetes-related death	0.61 (95% CI 0.40 to 0.94) p=0.03
	All-cause mortality	0.68 (95% CI 0.49 to 0.93) p=0.01
	Myocardial infarction	0.64 (95% CI 0.45 to 0.92) p=0.02
	Stroke	NS
	Peripheral vascular disease	NS
	Microvascular	NS
Non-UKPDS trials: metformin vs comparison	All-cause mortality	NS
	Ischaemic heart disease	NS

▷ Glucose control

Overall, the evidence appraised suggested that monotherapy with metformin produced significantly greater improvements in glycaemic control (i.e. HbA_{1c} and FPG/fasting blood glucose (FBG)) when it was compared with placebo, diet and sulfonylureas. Head-to-head comparisons with other antidiabetic agents (i.e. alpha-glucosidase inhibitors, thiazolidinediones, meglitinides and insulin) and extended-release formulations of metformin, failed to show more benefit for glycaemic control than standard monotherapy with metformin. In addition metformin used in combination with different doses of nateglinide produce significantly lower glycaemic values than metformin monotherapy.

▷ Body weight/body mass index

Overall, the evidence demonstrated a significant difference in terms of body weight/BMI reduction favouring metformin monotherapy when compared with sulfonylureas, glitazones and insulin therapies. Non-significant differences were found in head-to-head comparisons between metformin against placebo, diet, alpha-glucosidase inhibitors, meglitinides and treatment with extend-release formulation of metformin. Combination of metformin and different doses of nateglinide produced a significant reduction in body weight when compared with metformin monotherapy. **Level 1+**

▷ Lipid profile

Non-significant differences in terms of lipid profile were found when metformin was compared with placebo or meglitinides. **Level 1++**

Studies evaluating other comparisons found differences in specific lipid profile parameters.

When compared to diet, metformin significantly reduced total cholesterol (TC), however in a comparison with a α -glucosidase inhibitor, metformin significantly increased TC.⁵⁶ **Level 1++**

The meta-analysis of studies comparing metformin to sulfonylureas found significant benefits for metformin in terms of low-density lipoprotein cholesterol (LDL-C) and triglycerides.⁵⁶ **Level 1++**

In a comparison of metformin against insulin, significant benefits for metformin were found in terms of total and LDL-C levels but not high-density lipoprotein cholesterol (HDL-C).⁵⁶ **Level 1++**

In a study which compared metformin with pioglitazone,⁵⁹ pioglitazone was significantly more beneficial in terms of triglycerides and HDL-C, however metformin was more beneficial for LDL-C levels. The TC/HDL-C ratio did not differ significantly between the groups. **Level 1++**

A study which compared metformin monotherapy with metformin and nateglinide⁶³ found no differences across the lipid profile between these two groups except for triglycerides which were reduced significantly in the metformin and nateglinide group (nateglinide 120 mg tablets thrice daily). **Level 1+**

Where MIR was compared with MXR treatment, lipid profiles were similar between groups (statistical significance not reported) except for triglycerides where the mean change from baseline in the immediate-release group was 1 mg/dL; but was 34 mg/dl in the MXR 1,000 mg arm, and 42 mg/dl in the MXR 1,500 mg arm.⁶⁵ **Level 1+**

Table 9.2 Metformin comparison studies

Comparison	Study	Change in HbA _{1c} (%)		FPG	Post load glucose/PPBG/PPGE		BMI (kg/m ²)	Body weight (kg)	TC	LDL	TG	HDL				
		SMD	95% CI		NE	SMD							95% CI			
Head-to-head comparisons																
Metformin vs placebo	Cochrane systematic review ⁵⁶ 12 studies N=1,587	SMD -0.97	(95% CI -1.25 to -0.69)	SMD -0.87	(95% CI -1.13 to -0.61)	NE	NS	-	NS	Four studies N=906	NS	Three studies N=374	NS	Four studies N=418		
Metformin vs diet	Cochrane systematic review ⁵⁶ Three studies N=914	SMD -1.06	(95% CI -1.89 to -0.22)	NS		NE	NS	-	SMD -0.59	(95% CI -0.90 to -0.27)	NS	Two studies N=161	NS	One study N=61		
Metformin vs alpha-glucosidase inhibitors	Cochrane systematic review ⁵⁶ Two studies N=223	NS		NS		NE	NS	-	1.32	(95% CI 0.77 to 1.87)	NS	One study N=62	NS	One study N=62		
Metformin vs sulfonylureas	Cochrane systematic review ⁵⁶ 12 studies N=2,376	SMD -0.14	(95% CI -0.28 to -0.01)	SMD -0.16	(95% CI -0.27 to -0.05)	NE	SMD -0.45	(95% CI -0.80 to -0.10)	NS	10 studies N=1,150	SMD -0.29	(95% CI -0.52 to -0.07)	SMD -0.22	(95% CI -0.43 to -0.02)	NS	Eight studies N=1,069
Metformin vs meglitinides	Cochrane systematic review ⁵⁶ Two studies N=413	NS		SMD -0.31	(95% CI -0.51 to -0.12)	NE	NS	-	NS	One study N=56	NS	One study N=56	NS	One study N=56		

continued

Table 9.2 Metformin comparison studies – continued

Comparison	Study	Change in HbA _{1c} (%)	FPG	Post load glucose/PPBG/PPGE	BMI (kg/m ²)	Body weight (kg)	TC	LDL	TG	HDL
Head-to-head comparisons – continued										
Metformin vs glitazones	Cochrane systematic review ⁵⁶ Three studies N=260	SMD -0.28 (95% CI -0.52 to -0.03)	NS	NE	NS	-	NE	NE	NE	NE
Metformin vs pioglitazone	One study ⁵⁹ N=1,199	NS	-0.3 mmol/l, p=0.016 in favour of pioglitazone	NE	NE	Mean body weight increased by 1.9 kg compared to a decrease of 2.5 kg with metformin*	NS (TC/HDL-C ratio)	+0.27 mmol/l change from baseline for pioglitazone vs -0.12 mmol/l metformin p=0.001	-0.61 mmol/l change from baseline for pioglitazone vs -0.3 mmol/l metformin p=0.001	+0.16 mmol/l change from baseline for pioglitazone vs +0.08 mmol/l metformin p=0.001
Metformin vs insulin	Cochrane systematic review ⁵⁶ Two studies N=811	NS	NS	NE	SMD -0.91 (95% CI -1.44 to -0.37)	-	SMD -0.77 (95% CI -1.29 to -0.24)	SMD -0.83 (95% CI -1.35 to -0.30)	SMD NS One study N=60	SMD 0.65 (95% CI 0.13 to 1.17) One study N=60

continued

Table 9.2 Metformin comparison studies – continued

Comparison	Study	Change in HbA _{1c} (%)	FPG	Post load glucose/PPBG/PPGE	BMI (kg/m ²)	Body weight (kg)	TC	LDL	TG	HDL
Head-to-head comparisons – continued										
MIR vs MXR (MXR – 1,000 mg and 1,500 mg)	One study ⁶⁵ N=217	NS	Mean FPG concentrations increased in all three treatment groups at week 24. The mean increases were smaller in the MXR groups compared with the MIR group (statistical significance not reported)	NE	NE	NS	Change from baseline MIR –1 mg/dl, MXR 1,000 +2 mg/dl and –3 mg/dl MXR 1,500*	Change from baseline –4 mg/dl with MIR and –6 mg/dl in both MXR groups*	Change from baseline MIR +2 mg/dl, MXR 1,000 +1 mg/dl, MXR 1,000 and –1 mg/dl +34 mg/dl and +42 mg/dl MXR 1,500*	Change from baseline MIR +2 mg/dl, 1,000 mg/dl and –1 mg/dl MXR 1,500*
Rosiglitazone/ metformin (FDC) vs metformin	One study ⁶² N=569	Treatment difference –0.22% (95% CI –0.36 to –0.09%, p=0.001)	–18.3 mg/dL 95% CI –23.5 to –13.2; p<0.0001 in favour of rosiglitazone/ metformin	NE	NE	There was a mean size effect increase from baseline in the RSG/MET group (1.3 (0.22) kg) and a mean decrease in the MET group (–0.9 (0.26) kg)*	0.1% change from baseline for MET vs 10.7% RSG/ MET*	3.4% change from baseline for MET vs 14.5% RSG/ MET*	–8.5% change from baseline for MET vs 1.2% RSG/ MET*	–1.3% change from baseline for MET vs 4.1% RSG/ MET*

continued

Table 9.2 Metformin comparison studies – continued

Comparison	Study	Change in HbA _{1c} (%)	FPG	Post load glucose/ PPBG/ PPGE	BMI (kg/m ²)	Body weight (kg)	TC	LDL	TG	HDL
Head-to-head comparisons – continued										
Metformin vs metformin + nateglinide (60 mg and 120 mg)	One study ⁶³ N=467	Nateglinide 60 mg –0.36%, p=0.003 nateglinide 120 mg –0.51%, p<0.001	–0.8 mmol/l (p=< 0.01) in favour of metformin + nateglinide 120 mg	NE	NE	0.9 kg increase was observed in the nateglinide 120 mg-group (over that in the metformin group) (p<0.001)	NS	NS	Metformin plus nateglinide 120 mg vs metformin (mean difference –0.2 p=0.042)	NS
Combinations										
Metformin + insulin biphasic vs insulin biphasic	One study ⁶⁴ N=341	0.39%, p=0.007	NE	PPBG NS	NE	NS	NE	NE	NS	NS

MET, metformin; NE, not evaluated; NS, non-significant; PBG, postprandial blood glucose; PPGE, postprandial glucose excursion; RSG, rosiglitazone; SMD, standardised mean difference; TG, triglycerides
*Indicates statistical significance tests not reported/performed

▷ Adverse events

The main differences across all the different treatment groups were:

- the high frequency of gastrointestinal (GI) complaints reported by metformin-treated patients
- the high frequency of hypoglycaemic events reported by sulfonylurea-treated patients
- the high number of episodes of oedema reported by glitazone-treated patients
- the high number of cases of upper respiratory infection in patients treated with meglitinides.

Level 1+

In the only RCT⁶⁵ directly comparing MIR and MXR, more diarrhoea, flatulence and abdominal pain were experienced in the extended-release group whilst more or equivalent proportions of patients, experienced nausea/vomiting, headache and dyspepsia/heartburn in immediate-release group (significance tests not performed). In placebo-controlled studies, patients on MXR always experienced more GI AEs than those on placebo.⁶⁶ Level 1+

A retrospective chart review⁶⁷ found a significantly reduced frequency of GI AE in a cohort of patients when they were switched from MIR to MXR. A cohort of patients taking metformin for the first time also experienced less GI AEs if they were commenced on MXR rather than the immediate-release formulation. Level 2+

Table 9.3 Metformin adverse events

Comparison	Study	Size effect
Head-to-head comparisons		
Metformin vs placebo	Cochrane systematic review ⁵⁶	Hypoglycaemia NS GI discomfort NS Diarrhoea Two studies N=639 3.09 (95% CI 1.58 to 6.07)
Metformin vs diet	Cochrane systematic review ⁵⁶	Hypoglycaemia One study N=811 4.21 (95% CI 1.40 to 12.66)
Metformin vs alpha-glucosidase inhibitors	Cochrane systematic review ⁵⁶	GI discomfort Two studies N=223 0.26 (95% 0.07 to 0.91)
Metformin vs glitazones	Cochrane systematic review ⁵⁶	NE
Metformin vs pioglitazone	One study ⁵⁹ N=1,199	Diarrhoea* Metformin 11.1% Pioglitazone 3.2% Oedema* Metformin 1.7% Pioglitazone 4.5%

continued

Table 9.3 Metformin adverse events – *continued*

Comparison	Study	Size effect
Head-to-head comparisons – <i>continued</i>		
MIR vs MXR (MXR – 1,000 mg and 1,500 mg)	One study ⁶⁵ N=217	Hypoglycaemia* Metformin MIR 1.4% Metformin MXR 1,000 mg 1.3% For other AEs* (Metformin IR 500 mg BD vs Metformin XR 1,000 mg od) Diarrhoea 3% vs 5% Flatulence 1% vs 4% Abdominal pain 1% vs 4% Nausea/vomiting 4% vs 3% Headache 4% vs 4% Dyspepsia/heartburn 6% vs 3%
MXR 1,000 mg (protocol 1) or 500–2,000 mg (protocol 2) vs placebo	Two studies ⁶⁶	Protocol 1 All-cause AEs were reported by 59.5% of patients treated with placebo and by 63.5% of patients treated with MXR For GI AEs (placebo vs MXR) Abdominal pain 5.1% vs 7.5% Diarrhoea 5.1% vs 6.9% Nausea/vomiting 3.8% vs 9.4% Protocol 2 All-cause AEs were reported by 59.5% of patients treated with placebo and by 65.85% of patients treated any dosage of MXR For GI AEs (placebo vs MXR) Abdominal pain 2.6% vs 5.1% Diarrhoea 3.4% vs 12.9% Nausea/vomiting 1.7% vs 8.2%
MIR (mean dose 1,282 mg) vs MXR (mean dose 1,258 mg)	One cohort study ⁶⁷	Overall in the MXR vs MIR cohorts: frequency of any GI AEs within the first year of treatment NS. Patients switched from MIR to MXR: Frequency of any GI AEs 26.45% on MIR vs 11.71% after switching to MXR; p=0.0006) Frequency of diarrhoea 18.05% vs 8.29%; p=0.0084) Comparison of patients new to metformin treatment with either MIR or MXR % of patients reporting a GI AE during the first year of treatment with MIR 19.83% vs 9.23% MXR (p=0.04) Frequency of diarrhoea (13.5% vs 3.08, p=0.0169)

continued

Table 9.3 Metformin adverse events – continued

Comparison	Study	Size effect
Head-to-head comparisons – continued		
Rosiglitazone/metformin (FDC) vs metformin	One study ⁶² N=569	Hypoglycaemia* Metformin 0.4% Rosiglitazone/metformin 1% Diarrhoea* Metformin 14% Rosiglitazone/metformin 6% Oedema* Metformin 1% Rosiglitazone/metformin 3%
Metformin vs metformin + nateglinide (60 mg and 120 mg)	One study ⁶³ N=467	Hypoglycaemia* Placebo group 3.9% Nateglinide 60 mg 8.4% Nateglinide 120 mg 15.6% Diarrhoea* Placebo group 7.9% Nateglinide 60 mg 5.8% Nateglinide 120 mg 5.6% Upper respiratory infection* Placebo group 4.6% Nateglinide 60 mg 9.7% Nateglinide 120 mg 8.1%
* Indicates statistical significance tests not reported/performed		

▷ Lactic acidosis

A Cochrane review⁵⁷ looked at the risk of lactic acidosis in patients treated with metformin. There were no cases of fatal or non-fatal lactic acidosis reported. **Level 1+**

In addition, one RCT⁵⁸ did not find a significant difference in plasma lactate levels between metformin-treated patients and patients treated with other antidiabetic agents. **Level 1+**

9.2.4 Health economics evidence statements

The UKPDS included an analysis of intensive blood glucose control with metformin for overweight patients compared to conventional treatment primarily with diet. The study included 753 overweight (more than 120% ideal body weight) patients with newly diagnosed Type 2 diabetes from 15 hospital-based clinics in England, Scotland and Northern Ireland. Of these patients 342 were allocated to an intensive blood glucose control policy with metformin and 411 were allocated to conventional treatment, primarily with diet alone. The study was conducted from 1977 to 1991. The median follow-up period was 10.4 years.

In the conventional policy group the glycaemic goal was to obtain the lowest FPG attainable with diet alone. In the intensive policy group the aim was a FPG of less than 6.0 mmol/l by increasing the dose of metformin from 500 to 2,550 mg a day as required. Use of metformin for intensive blood glucose control in overweight patients was found to confer a 32% risk reduction

for any diabetes-related endpoint and a 42% risk reduction for diabetes-related deaths compared with a conventional policy.

Resource use was routinely collected as part of the study. Non-inpatient resource use data was collected using a questionnaire distributed between January 1996 and September 1997. The incremental costs reported in the analysis have the study protocol driven costs removed. These were replaced with a pattern of clinic visits reflecting general practitioner and specialist clinical opinion on the implementation of intensive policy.

Where a patient was still alive at the end of the follow-up, a simulation model was used to estimate the time from end of follow-up to death. It was assumed that there would be no continuation of benefit of therapy beyond the trial period in both evaluations.

The data was used in a cost-effectiveness analysis³⁴ and a cost-utility analysis.³³ Both evaluations showed intensive blood glucose control with metformin for overweight patients to be cost-saving compared to conventional treatment.

In the cost-utility analysis, within trial costs and projected costs were included. In the cost-effectiveness analysis only costs incurred during the trial period were included.

Table 9.4 Results: Clarke (2001)³⁴

	Mean cost per patient (1997 cost year)		Mean cost difference (95% CI) per patient
	Conventional	Metformin	
Total costs, 3% discount per year	£6,878	£6,607	-£271 (-£1,345, £801)
Total costs, 6% discount per year	£5,893	£5,635	-£258 (-£1,171, £655)

Table 9.5 Results: Clarke (2001)³⁴

	Mean (95% CI) life expectancy (years) per patient		Mean difference (95% CI) per patient
	Conventional	Metformin	Difference
Not discounted	21.3	22.3	1.0 (-0.0, 2.1)
3% discount per year	15.1	15.7	0.6 (0.0, 1.2)
6% discount per year	11.3	11.7	0.4 (0.0, 0.8)

Table 9.6 Results: Clarke (2005)³³

	Mean cost per patient (2004 cost year)		Mean cost difference (95% CI) per patient
	Conventional	Metformin	
Total cost of treatment (3.5%)	£16,941	£15,290	-£1,021 (-£4,291, £2,249)
Total cost of treatment (6%)	£12,798	£11,792	-£1,006 (-£3,251, £1,239)

Table 9.7 Results: Clarke (2005)³³

	Mean (95% CI) QALY per patient		Mean difference (95% CI) per patient
	Conventional	Metformin	
Mean QALYs per patient (not discounted)	16.44	17.32	0.88 (-0.54, 2.29)
3.5% discount rate	–	–	0.55 (-0.10, 1.20)
6% discount rate	–	–	0.40 (-0.01, 0.80)

In the cost-effectiveness model with costs and effects discounted at a 6% rate, there was a 71% probability that metformin would prove to be cost-saving compared with a conventional policy.³⁴

If additional costs of intensive policy with metformin were 50% more than assumed in the baseline estimates then the cost per life-year gained would be £948.

In the cost-utility model there was a 77% probability that metformin would prove to be cost-saving compared with a conventional policy.³³ Sensitivity analyses were performed for anti-diabetic therapy cost ($\pm 50\%$); standard practice costs ($\pm 50\%$); cost of complications ($\pm 50\%$); utility of one when free of complications; no treatment benefit and continuing benefit beyond the trial. Metformin was consistently shown to be a cost-reducing intervention.

9.3 Insulin secretagogues

9.3.1 Methodological introduction

A large volume of RCTs were identified in this area as the sulfonylurea and meglitinide drug classes include nine different agents (chlorpropamide, glibenclamide, gliclazide, glimepiride, glipizide, gliquidone, tolbutamide, nateglinide and repaglinide). Head-to-head comparisons with metformin were excluded as this is addressed in a previous question. Comparisons with the thiazolidinediones (the glitazones) were also excluded, as this will be addressed as part of a separate evidence review (see section 10.2).

Twenty-one studies were identified, four of which were excluded due to methodological limitations.^{76–79}

Table 9.8 The various comparisons made in the included RCTs

	Reference
Nateglinide vs placebo	80,81
Repaglinide vs placebo	82
Repaglinide vs nateglinide	83
Repaglinide vs glimepiride	84
Repaglinide vs glipizide	85
Repaglinide vs glibenclamide	8
Repaglinide + bedtime NPH vs gliclazide + bedtime NPH	87
Nateglinide + metformin vs repaglinide + metformin	88
Nateglinide + metformin vs glibenclamide + metformin	89
Nateglinide + metformin vs gliclazide + metformin	90
Nateglinide + metformin vs nateglinide vs metformin	91
Nateglinide + insulin glargine vs placebo + insulin glargine	92
Gliclazide modified release vs glimepiride	93
Gliclazide modified release vs gliclazide immediate release	94
Glimepiride vs metformin vs glimepiride + metformin	95
Glibenclamide vs insulin lispro	96

One cohort study on UKPDS data compared patients treated with diet alone vs sulfonylurea vs metformin vs insulin monotherapy.⁹⁷

There is a paucity of studies for some comparisons, for example there are no head-to-head studies of the sulfonylureas (excluding studies of gliclazide-modified release) and only one study which compares a meglitinide with a sulfonylurea.⁸⁴

Differing study populations, dose and titration regimens may limit direct comparison between studies.

9.3.2 Health economic methodological introduction

Thirteen papers were identified in the literature search. Of these, three were considered of good quality and relevant to the guideline. Two UKPDS papers were identified; a cost-utility analysis³³ and a cost-effectiveness⁹⁸ analysis of intensive blood glucose control.

Metformin monotherapy was compared with nateglinide plus metformin in the UK.⁷⁴

9.3.3 Evidence statements

▷ Metiglinides (repaglinide and nateglinide) vs placebo

Overall, metiglinides produced a significantly greater glycaemic control and a higher incidence of hypoglycaemic events when compared with placebo. No differences were found in terms of body weight and lipid profile.

Table 9.9 Nateglinide (120 mg) vs placebo				
1 study ⁸¹ N=47				
Level of evidence 1+				
HbA _{1c}	Nateglinide -3.6% Placebo +5.6% p=0.02			
FPG	NS			
Post load glucose/PPBG	NE			
Lipid profile	TC NS	LDL NS	TG NS	HDL NS
Body weight/BMI	BMI NE	Body weight NE		
AEs	AE data not reported			

Table 9.10 Nateglinide (30, 60, 120 mg) vs placebo				
1 study ⁸⁰ N=675				
Level of evidence 1+				
HbA _{1c}	Nateglinide relative to placebo (-0.26±0.05, -0.31±0.04, -0.39±0.05 for 30 mg, 60 mg and 120 mg respectively) were significant (p<0.001)			
FPG	Modest but statistically significant and dose-related reduction of FPG relative to placebo (p<0.001 vs placebo for all dose strengths)			
Post load glucose/PPBG	NE			
Lipid profile	TC NE	LDL NE	TG NE	HDL NE
BMI/body weight	BMI NE	Body weight NS		
AEs	Hypoglycaemia There was a dose-related increase in symptomatic hypoglycaemia but the incidence of confirmed hypoglycaemia in nateglinide-treated patients was much lower than symptomatic hypoglycaemia			
		Symptomatic	Confirmed	
	Placebo	4.9%	(1.2%)	
	30 mg nateglinide	12%	(2.4%)	
	60 mg nateglinide	11.4%	(4.0%)	
	120 mg nateglinide	22.8%	(5.3%)	

Table 9.11 Repaglinide vs placebo 1 study ⁸² N=408 Level of evidence 1+				
HbA _{1c}	Final HbA _{1c} levels were significantly greater for repaglinide monotherapy than nateglinide monotherapy (-1.57 vs -1.04%, p=0.002)			
FPG	Significantly greater efficacy for repaglinide than nateglinide (-57 vs -18 mg/dl, p<0.001)			
Post load glucose/PPBG	NS			
Lipid profile	TC NE	LDL NE	TG NE	HDL NE
BMI/body weight	BMI NE	Body weight Mean weight gains from baseline to study end were +1.8 kg for repaglinide and +0.7 kg for nateglinide, p=0.04		
AEs	The most common AEs (3–10% of patients in both groups) were upper respiratory tract infection, sinusitis, constipation, arthralgia, headache and vomiting but there was no notable difference in the pattern between the two groups Hypoglycaemia There were 7% of repaglinide patients who had minor hypoglycaemic episodes and 0% for nateglinide (this is 0.016 events per patient per months for repaglinide vs 0 for nateglinide p=0.3, NS)			

▷ Repaglinide vs nateglinide

When repaglinide was compared with nateglinide in people with Type 2 diabetes previously treated with diet and exercise:

- repaglinide and nateglinide had similar postprandial glycaemic effects. However, repaglinide was more effective than nateglinide in reducing HbA_{1c} and FPG values
- a greater weight gain (p=0.04) was seen in repaglinide-treated patients when compared to nateglinide-treated patients
- hypoglycaemic events were more frequently reported by patients receiving repaglinide (non-significant difference between the two groups).

Table 9.12 Repaglinide vs nateglinide1 study⁸³ N=150**Level of evidence 1+**

HbA _{1c}	Final HbA _{1c} levels were 0.99% lower in the repaglinide group than in the placebo group (p<0.001)			
FPG	There was a mean 1.44 mmol/l greater reduction in the repaglinide group compared with the placebo group (p<0.001)			
Post load glucose/PPBG	NE			
Lipid profile	TC NE	LDL NE	TG NE	HDL NE
BMI/body weight	BMI NE	Body weight NS		
AEs	The overall tolerability of repaglinide was similar to placebo excluding hypoglycaemic events Hypoglycaemia 17% of patients in the repaglinide group and 3% in the placebo group reported minor episodes of hypoglycaemia 3 repaglinide patients reported a total of 4 major hypoglycaemic events			

▷ Meglitinides vs sulfonylureas

In head-to-head comparisons with sulfonylureas, meglitinides failed to demonstrate better glucose control and led to a similar number of hypoglycaemic events. No significant differences were observed in terms of lipid profile and body weight reduction.

Table 9.13 Repaglinide vs glimepiride1 study⁸⁴ N=132**Level of evidence 1+**

HbA _{1c}	NS			
FPG	NS			
Post load glucose/PPBG	PPG levels were significantly lower with repaglinide compared with glimepiride (p<0.01)			
Lipid profile	TC NS	LDL NS	TG NS	HDL NS
BMI/body weight	BMI NS	Body weight NS		
AEs	AE data not reported			

Table 9.14 Repaglinide vs glipizide				
1 study ⁸⁵ N=256				
Level of evidence 1+				
HbA _{1c}	Statistically significant difference between HbA _{1c} changes from baseline in the two treatment groups in favour of repaglinide (0.19% vs 0.78%, difference -0.59%, p<0.05)			
FPG	Statistically significant difference between FPG changes in the two treatment groups in favour of repaglinide (0.5 mmol/l vs 1.3 mmol/l, difference -0.9 mmol/l, p<0.05)			
Post load glucose/PPBG	NE			
Lipid profile	TC NS	LDL NS	TG NS	HDL NS
BMI/body weight	BMI NE	Body weight NS		
AEs	<p>A total of 20 patients in the repaglinide group and nine in the glipizide group reported AEs other than hypoglycaemia. The most common were nausea and fatigue</p> <p>Hypoglycaemia</p> <p>The number of patients experiencing minor hypoglycaemic events was similar in the repaglinide and glipizide groups (15% vs 19% respectively)</p>			

Table 9.15 Repaglinide vs glibenclamide				
1 study ⁸⁶ N=175				
Level of evidence 1+				
HbA _{1c}	NS			
Fasting glucose	Glibenclamide caused a significantly greater decrease than repaglinide (p<0.001)			
PPG peak and 2 hour PPG levels	<p>Repaglinide caused a significantly greater decrease in peak glucose than glibenclamide (p<0.001)</p> <p>AUC 0-2h decreased significantly more among patients receiving repaglinide (p=0.01)</p>			
Lipid profile	TC NS	LDL NE	TG NS	HDL NS
BMI/body weight	BMI NE	Body weight NE		
AEs	Hypoglycaemic events; repaglinide (9%) and glibenclamide (13%)			
CIMT	CIMT regression was observed in 52% of patients receiving repaglinide and in 18% of those receiving glibenclamide (p<0.01)			
Inflammatory markers IL-6 and C-reactive protein	IL-6 and C-reactive protein decreased more in the repaglinide group than in the glibenclamide group (p=0.04 and p=0.02 respectively)			
AUC, area under curve; CIMT, carotid intima-media thickness				

▷ Gliclazide modified release vs gliclazide

When a modified-release version of gliclazide was compared with the immediate-release version of gliclazide in people with Type 2 diabetes who had been on diet control or on treatment with oral hypoglycaemic agents:

- both versions were associated with significant reductions in HbA_{1c} (non-significant difference between the two groups). FPG decreased significantly on gliclazide MR but not on gliclazide (non-significant difference between the two groups)
- no clinically significant changes were seen in terms of lipid profile (non-significant difference between the two groups)
- hypoglycaemic events were only reported by patients receiving gliclazide MR (9%) (non-significant difference was reported between the two groups).

Table 9.16 Gliclazide MR vs gliclazide

1 study⁹⁴ N=63

Level of evidence 1+

HbA _{1c}	NS			
FPG	NS			
Post load glucose/PPBG	NE			
Lipid profile	TC NE	LDL NE	TG NE	HDL NE
BMI/body weight	BMI NE	Body weight NS		
AEs	<p>In the gliclazide MR group, the most common adverse effects reported by patients were abdominal pain (9%) and pharyngitis (9%), while in the gliclazide group the most common adverse effect was neuropathy (14%)</p> <p>Hypoglycaemia Three patients (9.3%) experienced five mild hypoglycaemic episodes in the gliclazide MR treatment group. No suspected hypoglycaemic episodes were observed in the gliclazide treatment group</p>			

▷ Gliclazide MR vs glimepiride

When a modified-release version of gliclazide was compared with glimepiride in people with Type 2 diabetes being treated with diet alone or with either metformin or alpha-glucosidase inhibitors:

- both interventions were equally effective in terms of glycaemic control (alone or in combination with metformin or alpha-glucosidase inhibitors)
- gliclazide MR had a better safety profile than glimepiride.

Table 9.17 Gliclazide MR vs glimepiride				
1 study ⁹³				
Level of evidence 1+				
HbA _{1c}	NS			
FPG	NS			
Post load glucose/PPBG	NE			
Lipid profile	TC NS	LDL NS	TG NS	HDL NS
BMI/body weight	BMI NE	Body weight gliclazide MR: 83.1 to 83.6 kg glimepiride: 83.7 to 84.3 kg*		
AEs	Hypoglycaemia Hypoglycaemia with blood glucose <3 mmol/l occurred significantly less frequently (p=0.003) in the gliclazide MR group (3.7%) compared with the glimepiride group (8.9%) with an odds ration of 2.5 (95% CI, 1.4 to 4.7)			
* Indicates statistical significance tests between groups were not reported/performed				

▷ Insulin lispro vs glibenclamide

When insulin lispro was compared with glibenclamide in people with Type 2 diabetes who had been treated with oral antidiabetic (OAD) therapy, but not insulin:

- both regimes produced comparable effects in the control of glycaemia with respect to HbA_{1c}. However, treatment with insulin lispro resulted in smaller postprandial blood glucose excursions compared to oral treatment with glibenclamide
- no significant differences were observed between the treatment groups regarding hypoglycaemic episodes and other AEs.

Table 9.18 Insulin lispro vs glibenclamide				
1 study ⁹⁶ N=143				
Level of evidence 1+				
HbA _{1c}	NS			
FPG	NE			
Post load glucose/PPBG	The change in mean overall blood glucose excursions from baseline to endpoint was -1.0±1.5 mmol/l in the insulin lispro-treatment group and -0.3±1.5 mmol/l in the glibenclamide group, (p=0.013)			
Lipid profile	TC NE	LDL NE	TG NE	HDL NE
BMI/body weight	BMI NE	Body weight NS		
AEs	AEs No significant difference between groups Hypoglycaemia No significant difference between groups			

▷ Bedtime NPH + repaglinide vs bedtime NPH + gliclazide

When repaglinide was compared with gliclazide (both drugs in combination with bedtime NPH) in Type 2 diabetes patients inadequately controlled with oral hypoglycaemic therapy:

- both interventions were associated with significant reductions in HbA_{1c} and FPG (non-significant difference between the two groups)
- weight gain during the treatment period was similar in both groups
- no significant differences were observed between the treatment groups regarding hypoglycaemic episodes and other AEs.

Table 9.19 Bedtime NPH + repaglinide vs bedtime BPH + gliclazide

1 study⁸⁷ N=80

Level of evidence 1++

HbA _{1c}	NS			
FPG	NS			
Post load glucose/PPBG	N			
Lipid profile	TC NE	LDL NE	TG NE	HDL NE
BMI/body weight	BMI NE	Body weight NS		
AEs	AEs A total of 70 AEs were recorded throughout the study, 38 in the insulin/gliclazide and 32 in the insulin/repaglinide group. Hypoglycaemia No significant difference between groups			

▷ Nateglinide + metformin vs gliclazide + metformin

Nateglinide in combination with metformin was compared with gliclazide and metformin, to compare the effects on glycaemic control in patients with Type 2 diabetes:

- no significant difference was seen between the groups in terms of HbA_{1c}
- the nateglinide group demonstrated better PPG control.

Table 9.20 Nateglinide + metformin vs gliclazide + metformin				
1 study ⁹¹ N=262				
Level of evidence 1+				
HbA _{1c}	NS			
FPG	NS			
Post load glucose/PPBG		Nateglinide + metformin	Gliclazide + metformin	p-value
	Max PPG excursion (mmol/l)	-0.71±0.22	-0.10±0.23	p=0.037
	30 minute postprandial insulin (pmol/l)	98.9±12.1	32.5±12.56	p<0.001
	2 hour postprandial insulin (pmol/l)	83.9±16.6	39.6±17.8	p=0.047
	2 hour postprandial insulin excursion (pmol/l)	75.5±16.0	30.2±16.6	p=0.033
Lipid profile	TC NE	LDL NE	TG NE	HDL NE
BMI/body weight	BMI NE	Body weight NS		
AEs	Suspected drug-related AEs Nateglinide arm 6.9% Gliclazide arm 7.1% NS			

▷ Glimepiride + metformin vs glimepiride vs metformin

When glimepiride in combination with metformin was compared with monotherapy of each drug in Type 2 diabetes patients inadequately controlled by metformin monotherapy:

- combination treatment was more effective than either drug alone in terms of glycaemic control
- combination therapy was more effective than either drug in reducing TC levels
- metformin alone resulted in a significantly lower BMI than either glimepiride alone, or the combination
- the incidence of hypoglycaemic episodes was significantly higher in the combination treatment group than in either of the monotherapy groups.

Table 9.21 Glimepiride vs metformin vs glimepiride + metformin1 study⁹⁵ N=372

Level of evidence 1++

HbA _{1c}	Combination treatment (glimepiride + metformin) was significantly more efficient in reducing HbA _{1c} levels than: glimepiride alone (difference in mean change 1.04% 95% CI 0.81 to 1.27%; p<0.001) metformin alone (difference in mean change 0.92% 95% CI 0.63 to 1.21%; p<0.001) There was no significant difference between metformin or glimepiride monotherapy in terms of HbA _{1c}															
FPG	Combination treatment was significantly more effective than either monotherapy in reducing FBG (p<0.001) There was no significant difference between metformin or glimepiride monotherapy in terms of FPG															
Post load glucose/PPBG	Combination treatment was significantly more effective than either monotherapy in reducing PPBG (p<0.001) Treatment with glimepiride was significantly more effective than metformin in reducing PPBG (p<0.001)															
Lipid profile	TC Combination was significantly more effective than glimepiride alone (p<0.001) in reducing TC levels, although there was no significant difference between the combination and metformin alone	LDL NS	TG NS	HDL NS												
BMI/body weight	BMI Treatment with metformin resulted in a significantly lower BMI than either glimepiride alone (p<0.001) or the combination treatment (p<0.002); however there was NS difference between the glimepiride and combination treatment groups	Body weight NE														
AEs	<p>AEs were experienced by 105 patients</p> <table border="1"> <thead> <tr> <th></th> <th>N</th> <th>(%)</th> </tr> </thead> <tbody> <tr> <td>Metformin</td> <td>22</td> <td>(29%)</td> </tr> <tr> <td>Glimepiride</td> <td>38</td> <td>(25%)</td> </tr> <tr> <td>G + M</td> <td>45</td> <td>(31%)</td> </tr> </tbody> </table> <p>Hypoglycaemia The incidence of symptomatic episodes was significantly higher in the combination treatment group than in either of the monotherapy groups (22% of patients vs 11% of patients in the metformin group and 13% of patients in the glimepiride group, p=0.039) Diarrhoea was more commonly reported in the metformin group than in the other two treatment groups (7% of patients vs 1% of patients in the glimepiride group and 3% of patients in the combination group)</p>					N	(%)	Metformin	22	(29%)	Glimepiride	38	(25%)	G + M	45	(31%)
	N	(%)														
Metformin	22	(29%)														
Glimepiride	38	(25%)														
G + M	45	(31%)														

▷ Nateglinide + metformin vs nateglinide vs metformin vs placebo

When nateglinide in combination with metformin was compared with monotherapy of each treatment and placebo in drug naive patients with Type 2 diabetes:

- nateglinide, metformin and combination therapy (nateglinide + metformin), were associated with significant reductions in HbA_{1c}, FPG and PPGE (an additive effect was seen with combination therapy)
- the incidence of GI AEs was higher in patients receiving combination therapy and metformin than in those receiving placebo and nateglinide
- the incidence of hypoglycaemic episodes was higher in the combination treatment group than in either of the monotherapy groups.

Table 9.22 Nateglinide vs metformin vs nateglinide + metformin
1 study⁹¹ N=401
Level of evidence 1+

HbA _{1c}	Changes from baseline			
	Placebo	(Δ = +0.3±0.1%)		
	Nateglinide	(Δ = -0.8±0.1%)		
	Metformin	(Δ = -0.8±0.1%)		
	Combination therapy	(Δ = -1.6±0.1%)		
FPG	Changes from baseline			
	Placebo	not change		
	Nateglinide	(Δ = -1.1±0.3 mmol/l)		
	Metformin	(Δ = -1.2±0.3 mmol/l)		
	Combination therapy	(Δ = -2.3±0.3 mmol/l)		
Post load glucose/PPBG	Changes from baseline			
	Placebo	(Δ = -0.5±0.2 mmol/l)		
	Metformin	(Δ = -1.0±0.2 mmol/l)		
	Nateglinide	(Δ = -1.9±0.2 mmol/l)		
	Combination therapy	(Δ = -2.3±0.2 mmol/l)		
Lipid profile	TC	LDL	TG	HDL
	NE	NE	NE	NE
BMI/body weight	BMI	Body weight		
	NE	NS changes from baseline for combination therapy (Δ = +0.2±0.4 kg) placebo (Δ = -0.2±0.4 kg)		
AEs	No serious AEs judged to be related to study medication			
	GI			
	The percentage of patients randomised to combination therapy experiencing one or more GI AE (27%) was essentially identical to that of those receiving metformin monotherapy (27.9%), and approximately twofold that of patients receiving placebo and nateglinide monotherapy (14.4% and 16.3% respectively)			
	Incidence of symptomatic hypoglycaemia in patients receiving combination therapy=29%			
	Incidence of confirmed hypoglycaemia in drug naive patients receiving combination therapy 3.4% (with all considered to be mild)			

▷ Nateglinide + insulin glargine vs placebo + insulin glargine

The effect of adding nateglinide to therapy with insulin glargine in adults with Type 2 diabetes previously treated with insulin and with poor blood glucose control.

- Adding nateglinide improved blood glucose control in the early part of the day after breakfast and lunch.
- Adding nateglinide did not provide good blood glucose control overall.

Table 9.23 Nateglinide + insulin vs placebo + insulin glargine

1 study⁹¹ N=55

Level of evidence 1+

HbA _{1c}	NS			
Post load glucose/PPBG	Self-monitored blood glucose concentrations (mmol/l) were significantly lower in the nateglinide group only at certain times of the day.			
	Difference in mmol/l			
	Time	(95% CI)	p-value	
	After breakfast	-2.3 (-4.4, 0.2)	0.030	
	Before lunch	-2.5 (-4.6, -0.3)	0.029	
	After lunch	-2.3 (-4.6, -0.4)	0.021	
Lipid profile	TC NE	LDL NE	TG NE	HDL NE
BMI/body weight	BMI NE	Body weight NS		
AEs	NS			

▷ Diet vs sulphonylurea vs insulin

This cohort study investigated the incidence of hypoglycaemia in patients treated with diet alone, sulphonylurea, metformin or insulin monotherapy. The results on metformin are not discussed here as they are considered in a separate question.

Table 9.24 Diet vs sulphonylurea vs insulin
1 study⁹⁷ N=5,063
Level of evidence 2+

HbA _{1c}	NE			
FPG	NE			
Post load glucose/PPBG	NE			
Lipid profile	TC NE	LDL NE	TG NE	HDL NE
BMI/body weight	BMI NE	Body weight NE		
AEs	Annual percentage (95% CI) of patients reporting at least one hypoglycaemic episode in relation to therapy			
		Grades 1–4 hypoglycaemia	Grades 2–4 hypoglycaemia	
	Therapy			
	Diet alone	0.8 (0.6 to 1.0)	0.1 (0.1 to 0.2)	
	Sulphonylurea	7.9 (5.1 to 11.9)	1.2 (0.4 to 3.4)	
Basal insulin alone	21.2 (14.6 to 29.8)	3.8 (1.2 to 11.1)		
Basal + prandial insulin	32.6 (21.8 to 45.6)	5.5 (2.0 to 14.0)		
Hypoglycaemia was defined on the following scale: 1) transitory symptoms not affecting normal activity 2) temporarily incapacitated but patient able to control symptoms without help 3) incapacitated and required assistance to control symptoms without help 4) required medical attention or glucagon injection				

9.3.4 Health economic evidence statements

▷ Sulphonylurea monotherapy

Conventional glucose control, mainly through diet was compared to more intense blood glucose control with insulin or sulphonylureas in the UKPDS. Intensive treatment was cost-saving with the resource use according to the trial protocol. Using standard clinical resource use, intensive treatment had an incremental cost-effectiveness ratio (ICER) of £1,166 per event-free year gained within the trial period (6% discount rate, 1997 cost year).⁹⁸

In a further cost-utility analysis published in 2005 intensive blood glucose control with insulin or sulphonylurea was found to have a cost-effectiveness ratio of £6,028 per QALY gained compared to conventional glucose (2004 cost year, 3.5%).³³

▷ Combination therapy

Metformin monotherapy (1,500 mg/day) was compared with nateglinide (360 mg/day) plus metformin (1,500 mg/day) in a UK setting. A hypothetical population based on US data was used. The mean baseline HbA_{1c} level was 8.4%. The duration of diabetes was not stated, although a pre-model period of 7 years was included. The resulting cost per QALY was £8,058 (1999 cost year, 3% discount rate).⁷⁴

9.4 Acarbose

9.4.1 Methodological introduction

A Cochrane review⁹⁹ and eight RCTs^{100–107} compared monotherapy acarbose or other combination OAD drugs, with other OAD drug regimens or placebo. Studies were excluded unless they were of at least 12-weeks duration. Two of the RCTs^{100,107} were excluded due to methodological limitations.

The Cochrane review⁹⁹ identified 30 RCTs in a search performed in April 2003 which compared acarbose monotherapy with placebo, sulfonylureas, metformin or nateglinide. The additional six RCTs included in this analysis compared acarbose with placebo when both groups were also treated with metformin,¹⁰⁴ with sulphonylureas,^{105,106} or with insulin,¹⁰³ and there were also comparisons between acarbose and pioglitazone¹⁰¹ and acarbose and sulfonylurea.¹⁰²

Although a substantial amount of evidence has been found in this area, several different drug combinations and comparisons, differing dosing and titration regimens and the differing populations included in the studies, limit direct comparison between studies. Additionally, some study results may not be generalisable to a UK population of people with Type 2 diabetes. For example, the study by Lin¹⁰⁶ was undertaken in a Chinese population with a mean BMI of 25 kg/m².

9.4.2 Health economic methodological introduction

Three papers were identified from the literature search. All three were excluded. One was an analysis of adherence to oral antihyperglycaemic medication conducted in the US. This was not an economic analysis, and the comparison of costs was of patients with diabetes compared to patients with diabetes and cardiovascular disease.¹⁰⁸

One paper was a cost-effectiveness analysis with an outcome of prevention of progression to Type 2 diabetes, which is outside of the scope of these guidelines.¹⁰⁹

The final paper identified was a cost-effectiveness analysis. The focus was on quality of life in older patients. Not enough description was given of the treatments, referring only to oral medication with no further details.¹¹⁰

9.4.3 Evidence statements

The evidence appraised suggested that acarbose (used as monotherapy or in combination) failed to demonstrate better glycaemic control when compared with other oral agents. Treatment with acarbose did not demonstrate superiority over other oral agents when lipid profile and body weight were evaluated.

Reports of adverse effects were higher in the acarbose groups across all studies.^{99,101–106} The main difference between the treatment groups was the high frequency of GI complaints reported by acarbose-treated patients. Flatulence was reported in all acarbose arms ranging from 28.6% to 57.5% of all patients.

Table 9.25 HbA_{1c}

Comparison	Study	Change in HbA _{1c} (%)
Acarbose vs placebo	Cochrane systematic review ⁹⁹ 28 studies N=2,831	-0.77, 95% CI -0.90 to -0.64
Acarbose vs metformin	Cochrane systematic review ⁹⁹ One study N=62	NS
Acarbose vs sulfonylurea	Cochrane systematic review ⁹⁹ Eight studies N=596	NS
	One study ¹⁰² N=219	Greater reduction in HbA _{1c} in the glimepiride group (2.5±2.2%) compared with the acarbose group (1.8±2.2%, p=0.014)
Acarbose vs pioglitazone	One study ¹⁰¹ N=271	Greater reduction for the patients treated with pioglitazone compared with those treated with acarbose (p<0.001)
Acarbose vs nateglinide	Cochrane systematic review ⁹⁹ One study N=179	NS
Acarbose + metformin vs placebo + metformin	One study ¹⁰⁴ N=83	LSM* difference between the treatment arms of 1.02%, 95% CI 0.543 to 1.497%, p=0.0001
Acarbose + sulfonylurea vs placebo + sulfonylurea	One study ¹⁰⁶ N=69	The difference in the mean endpoints between the two treatment groups was -1.05%, 95% CI -1.69 to -0.41, p=0.0018
	One study ¹⁰⁵ N=373	LSM difference -0.54%, CI -0.86 to -0.22; p=0.001)
Insulin + acarbose vs insulin + placebo	One study ¹⁰³ N=112	Comparison between the treatment groups showed a difference of -0.69%, 95% CI -1.18 to -0.20; p=0.008

*Adjusted least square mean

LSM, least square mean; NS, non-significant; PP, postprandial

