Healthcare Improvement Scotland

SIGN

SIGN 154 • Pharmacological management of glycaemic control in people with type 2 diabetes

A national clinical guideline

November 2017

Evidence

KEY TO EVIDENCE STATEMENTS AND RECOMMENDATIONS

LEVELS OF EVIDENCE

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

RECOMMENDATIONS

Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the 'strength' of the recommendation).

The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher-quality evidence is more likely to be associated with strong recommendations than lower-quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation.

Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence, and the balance of benefits and harms of the options.

R For '**strong**' recommendations on interventions that '**should**' be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more good than harm. For **'strong'** recommendations on interventions that **'should not'** be used, the guideline development group is confident that, for the vast **majority** of people, the intervention (or interventions) will do more harm than good.

R For **'conditional'** recommendations on interventions that should be '**considered**', the guideline development group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.

GOOD-PRACTICE POINTS

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

NICE accredited
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NICE has accredited the process used by Scottish Intercollegiate Guidelines Network to produce clinical guidelines. The accreditation term is valid until 31 March 2020 and is applicable to guidance produced using the processes described in SIGN 50: a guideline developer's handbook, 2015 edition (www.sign.ac.uk/guidelines/fulltext/50/index.html). More information on accreditation can be viewed at www.nice.org.uk/accreditation

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Scottish Intercollegiate Guidelines Network

Pharmacological management of glycaemic control in people with type 2 diabetes

A national clinical guideline

November 2017

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www.sign.ac.uk

First published November 2017

ISBN 978 1 909103 61 0

Citation text

Scottish Intercollegiate Guidelines Network (SIGN).
Pharmacological management of glycaemic control in people with type 2 diabetes. Edinburgh: SIGN; 2017.
(SIGN publication no. 154). [November 2017]. Available from URL: http://www.sign.ac.uk

Contents

1 Introduction

1.1 THE NEED FOR A GUIDELINE

The immediate purpose of lowering blood glucose in people with type 2 diabetes is to provide relief from symptoms (thirst, polyuria, nocturia, and blurred vision). Thereafter, the aim is to prevent microvascular complications: loss of vision (retinopathy), renal failure (nephropathy), and foot ulceration (neuropathy). High blood glucose (hyperglycaemia) is also one of the features of diabetes, along with raised blood pressure and cholesterol, which is associated with macrovascular complications (myocardial infarction, stroke, and peripheral arterial disease).

The effects of glucose-lowering therapies on cardiovascular morbidity and mortality are therefore of major importance and not necessarily related to glucose lowering. Until 2010, the majority of clinical trials focused narrowly on glucose control (as assessed by HbA1c (glycated haemoglobin) concentrations), and on the risks of weight gain and hypoglycaemia rather than on cardiovascular morbidity and mortality. Since then, several large cardiovascular outcome trials have been published comparing individual glucose-lowering agents with standard of care (individually described within this guideline). Almost all were initiated in response to changes in regulatory requirements, initially in the USA and subsequently in Europe, that were introduced in 2008 following controversy regarding the safety of the thiazolidinedione agent rosiglitazone.[1]

1.1.1 UPDATING THE EVIDENCE

Some of the content in this guideline was originally published in section 6 of SIGN 116: Management of diabetes.[2]

Given the significant volume of new evidence relating to pharmacological treatment of glucose lowering in people with type 2 diabetes that has been published since SIGN 116 was issued in 2010, and to support the publication of a revised Scottish Diabetes Prescribing Strategy, this update is published as a stand-alone guideline.

Other than the addition of a single new meta-analysis which pools results from RCTs that were already included in the current guideline, section 3 describing targets for glycaemic control was not updated and text and recommendations in this section are reproduced verbatim from SIGN 116. The original supporting evidence was not re-appraised by the current guideline development group.

This guideline was developed as a rapid update using an adaptation to SIGN's standard methodology. This approach used evidence from five sources: the existing guideline published as a chapter of SIGN 116, a comprehensive series of systematic reviews and meta-analyses developed by the Agency of Healthcare Research and Quality (AHRQ), published in 2016,[3] the National Institute for Health and Care Excellence (NICE) clinical guideline on type 2 diabetes in adults, published in 2015,[4] new searches for primary literature carried out to update these sources to November 2016 and finally, cardiovascular outcome trials published during the development period of the guideline (up to September 2017). Further information about the SIGN systematic review can be found in section 14.1.

1.2 REMIT OF THE GUIDELINE

1.2.1 OVERALL OBJECTIVES

This guideline provides evidence-based recommendations and best practice guidance on: (i) optimal targets for glucose control for the prevention of microvascular and macrovascular complications, which remain consistent with advice first published in SIGN 116; and (ii) the risks and benefits of the principal therapeutic classes of glucose-lowering agents and insulins currently available for those who require measures beyond diet and exercise to achieve glucose targets, which have been updated from SIGN 116. An updated algorithm to guide the choice of first-, second- and third-line glucose-lowering agent, which incorporates the summarised evidence and the clinical experience of the guideline development group, is included.

While lifestyle interventions, including appropriate diet, physical activity, blood glucose monitoring and other behaviours are vital to self management in people with type 2 diabetes, these are outwith the remit of this guideline. Further information on these topics can be found in SIGN 116.[2]

The management of glucose control in the dying patient with type 2 diabetes is also excluded from the remit of this document.

1.2.2 SUMMARY OF UPDATES TO THE GUIDELINE, BY SECTION

1.1	The need for a guideline	New
1.2	Remit of the guideline	New
2	Key recommendations	New
3	Targets for glycaemic control	Minor update
4.1	Metformin – glycaemic control	Updated
4.2	Metformin – hypoglycaemia, weight gain and adverse effects	Updated
4.3	Metformin – cardiovascular morbidity and mortality	Minor update
5.1	Sulphonylureas – glycaemic control	Updated
5.2	Sulphonylureas – hypoglycaemia, weight gain and adverse effects	Updated
5.3	Sulphonylureas – cardiovascular morbidity and mortality	Updated
6.1	Pioglitazone	Updated
6.2	Rosiglitazone	Completely revised
7.1	Dipeptidyl peptidase-4 inhibitors – glycaemic control	Updated
7.2	Dipeptidyl peptidase-4 inhibitors – hypoglycaemia, weight gain and adverse effects	Updated
7.3	Dipeptidyl peptidase-4 inhibitors – cardiovascular morbidity and mortality	Completely revised
8	Sodium glucose co-transporter 2 inhibitors	New
9.1	Glucagon-like peptide-1 receptor agonists – glycaemic control	Updated
9.2	Glucagon-like peptide-1 receptor agonists – hypoglycaemia, weight gain and adverse effects	Updated
9.3	Glucagon-like peptide-1 receptor agonists – cardiovascular morbidity and mortality	Completely revised
10.1	Continuing oral agents when initiating basal insulin	Updated
10.2	Choosing basal insulin	Updated
10.3	Insulin initiation and intensification	Minor update
11	Algorithm for glucose lowering	Completely revised
12.1	Checklist for provision of information	Updated

Following the results of the Acarbose Cardiovascular Evaluation (ACE) trial which showed no differences between participants taking acarbose and placebo for any cardiovascular outcomes, but significantly more adverse effects with acarbose,[5] and informed by the knowledge that only 0.1–0.2% of people who were prescribed antidiabetic drugs in Scotland in 2016–2017 received acarbose[6] the section on alpha-glucosidase inhibitors has been omitted.

1.2.3 TARGET USERS OF THE GUIDELINE

This guideline will be of interest to healthcare professionals involved in the management of people with type 2 diabetes, including diabetologists, diabetes specialist nurses, general practitioners, pharmacists and practice nurses as well as people with type 2 diabetes, carers, voluntary organisations and policy makers.

1.3 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results.

The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at through a process of shared decision making with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be documented in the patient's medical records at the time the relevant decision is taken.

1.3.1 INFLUENCE OF FINANCIAL AND OTHER INTERESTS

It has been recognised that financial interests in, or close working relationships with, pharmaceutical companies may have an influence on the interpretation of evidence from clinical studies.

It is not possible to completely eliminate any possible bias from this source, nor even to quantify the degree of bias with any certainty. SIGN requires that all those involved in the work of guideline development should declare all financial interests, whether direct or indirect, annually for as long as they are actively working with the organisation. By being explicit about the influences to which contributors are subjected, SIGN acknowledges the risk of bias and makes it possible for guideline users or reviewers to assess for themselves how likely it is that the conclusions and guideline recommendations are based on a biased interpretation of the evidence.

Signed copies are retained by the SIGN Executive and a register of interests is available in the supporting material section for this guideline at **www.sign.ac.uk**

1.3.2 PRESCRIBING OF LICENSED MEDICINES OUTWITH THEIR MARKETING AUTHORISATION

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation also known as product licence. This is known as 'off-label' use.

Medicines may be prescribed 'off label' in the following circumstances:

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

An unlicensed medicine is a medicine which does not have marketing authorisation for medicinal use in humans.

Generally 'off-label' prescribing of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the marketing authorisation. Such use should be supported by appropriate evidence and experience.[7]

"Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability".[7]

The General Medical Council (GMC) recommends that when prescribing a medicine 'off label', doctors should:

- be satisfied that such use would better serve the patient's needs than an authorised alternative (if one exists)
- be satisfied that there is sufficient evidence/experience of using the medicines to show its safety and efficacy, seeking the necessary information from appropriate sources
- record in the patient's clinical notes the medicine prescribed and, when not following common practice, the reasons for the choice
- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine.

Non-medical prescribers should ensure that they are familiar with the legislative framework and their own professional prescribing standards.

Prior to any prescribing, the licensing status of a medication should be checked in the summary of product characteristics (SPC).[8] The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers.[9]

1.3.3 HEALTH TECHNOLOGY ASSESSMENT ADVICE FOR NHSSCOTLAND

Specialist teams within Healthcare Improvement Scotland issue a range of advice that focuses on the safe and effective use of medicines and technologies in NHSScotland.

The Scottish Medicines Consortium (SMC) provides advice to NHS boards and their Area Drug and Therapeutics Committees about the status of all newly-licensed medicines, all new formulations of existing medicines and new indications for established products. NHSScotland should take account of this advice and ensure that medicines accepted for use are made available to meet clinical need where appropriate.

Until 1 October 2017, Healthcare Improvement Scotland reviewed Multiple Technology Appraisals (MTAs) produced by the National Institute for Health and Care Excellence (NICE) and provided advice about their applicability in NHSScotland. If Healthcare Improvement Scotland has advised that MTA guidance was applicable in Scotland, NHSScotland should take account of this and ensure that recommended medicines and treatment are made available to meet clinical need where appropriate.

NICE MTAs deemed valid for NHSScotland supersede extant SMC advice as they are generally underpinned by a larger and more recent evidence base.

SMC advice and NICE MTA guidance relevant to this guideline are summarised in section 13.

2 Key recommendations

The following were highlighted by the guideline development group as the key clinical recommendations that should be prioritised for implementation.

2.1 TARGETS FOR GLYCAEMIC CONTROL

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

2.2 METFORMIN

R **Metformin should be considered as the first-line oral treatment option for people with type 2 diabetes.**

2.3 SODIUM GLUCOSE CO-TRANSPORTER 2 INHIBITORS

R **In individuals with type 2 diabetes and established cardiovascular disease, SGLT2 inhibitors with proven cardiovascular benefit** (currently empagliflozin and canagliflozin) **should be considered.**

2.4 GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

R **For individuals with type 2 diabetes and established cardiovascular disease, GLP-1 receptor agonist therapies with proven cardiovascular benefit** (currently liraglutide) **should be considered.**

3 Targets for glycaemic control

3.1 TREATING TO GLYCAEMIC TARGETS

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

The United Kingdom Prospective Diabetes Study 33 (UKPDS 33) examined the effects of sulphonylureas, metformin and insulin over a median 10 year period in people with newly diagnosed diabetes. Mean HbA1c was lowered to 7.0% (53 mmol/mol) in the intensive arm compared to 7.9% (63 mmol/mol) in the conventional treatment group.[10] In UKPDS 34, HbA1c was lowered to 7.4% (57 mmol/mol) in a subgroup of overweight people who were randomised to metformin compared with 8.0% (64 mmol/mol) in the conventional therapy group.[11] **1+**

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study used modified-release (MR) gliclazide then increased metformin, thiazolidinedione, acarbose and insulin (initial basal with prandial added as required) to reduce HbA1c to a mean of 6.5% (48 mmol/mol) compared with a mean of 7.3% (56 mmol/mol) from a baseline of 7.5% (58 mmol/mol) by aiming for a target of <6.5% (48 mmol/mol) as compared with standard care. Mean duration of diabetes in this trial was 7.9 years.[12] **1+**

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study used the standard range of presently available therapy (including sulphonylureas, metformin, thiazolidinediones, insulin, dipeptidyl peptidase-4 (DPP-4) inhibitors and exenatide) to reduce HbA1c rapidly to a mean of 6.4% (46 mmol/mol) compared with a mean of 7.5% (58 mmol/mol) from a baseline of 8.3% (67 mmol/mol) by aiming for a target of 6.0% (42 mmol/mol) as compared with a target of 7.0 to 7.9% (53 to 63 mmol/mol). Mean duration of diabetes in this trial was 10 years.[13] **1+**

The Veterans Affairs Diabetes Trial (VADT) compared an intensive treatment strategy (maximal doses of metformin and rosiglitazone for people with body mass index (BMI) ≥27 kg/m^2; maximal doses of glimepiride and rosiglitazone for people with BMI <27 kg/m^2; insulin added in if HbA1c >6% (42 mmol/mol)) with a standard treatment strategy (half maximal doses of same agents; insulin added in if HbA1c >9% (74.9 mmol/mol)) in males with type 2 diabetes and baseline HbA1c 9.4% (79.2 mmol/mol). Achieved HbA1c levels were 6.9% (51.9 mmol/mol) and 8.4% (68.3 mmol/mol), respectively. Mean duration of diabetes in this trial was 11.5 years.[14] **1+**

3.2 MORTALITY

Reducing blood glucose to specific mean HbA1c targets did not significantly reduce mortality during follow up in most RCTs; however, there was a 36% relative risk reduction (95% confidence interval (CI) 9% to 55%) in all-cause mortality associated with intensive metformin treatment in UKPDS 34.[11] In the study (ACCORD) with the lowest mean HbA1c attained in the intensive treatment group (6.4% (46 mmol/mol)), treatment was stopped early as mortality in this group was significantly higher than in the usual care group (hazard ratios, HR 1.22, 95% CI 1.01 to 1.46 for all-cause mortality; and 1.35, 95% CI 1.04 to 1.76 for cardiovascular disease mortality).[13] The excess mortality may have occurred as a consequence of rapid reduction of HbA1c rather than the absolute value attained but there is no evidence to show that more gradual reduction of HbA1c to the same target is associated with lower mortality. **1+**

Ten-year follow up of UKPDS 33 and 34 suggested a long-term beneficial effect of more intensive glycaemic control in the early years after diagnosis of diabetes despite similar control in intensive and conventional groups after study close.[15] Reductions in all-cause mortality were reported for people treated with sulphonylurea or insulin (relative risk (RR) 13%, p=0.007) and for people treated with metformin (RR 27%, p=0.002). **2+**

3.3 CARDIOVASCULAR RISK

Two meta-analyses of the heterogeneous trials mentioned above have used different approaches to compare the effect of improved glycaemic control (reflected by achieved HbA1c of 6.4 to 7.0% (46.4 to 53.0 mmol/mol) in the intervention groups, compared with 7.3 to 8.4% (56.2 to 68.3 mmol/mol) in the control groups). One meta-analysis, using summary data and including the UKPDS metformin substudy, reported that intensive glycaemic control reduced the risk for cardiovascular disease (RR 0.90, 95% CI 0.83 to 0.98) but did not reduce the risk for all-cause mortality (RR 0.98, 95% CI 0.84 to 1.15), cardiovascular mortality (RR 0.97, 95% CI 0.76 to 1.24) or stroke (RR 0.98, 95% CI 0.86 to 1.11).[16] The other meta-analysis, using individual level data and excluding the UKPDS metformin substudy, reported that intensive glycaemic control reduced the risk for major cardiovascular disease (HR 0.91, 95% CI 0.84 to 0.99), mainly because of a 15% reduced risk of myocardial infarction (HR 0.85, 95% CI 0.76 to 0.94), but did not reduce the risk for all-cause mortality (HR 1.04, 95% CI 0.90 to 1.20), cardiovascular mortality (HR 1.10, 95% CI 0.84 to 1.42), stroke (HR 0.96, 95% CI 0.83 to 1.1) or hospitalised/fatal heart failure (HR 1.00, 95% CI 0.86 to 1.16).[17] **1++**

3.4 MICROVASCULAR MORBIDITY

Several RCTs showed that reduction of HbA1c to a mean level of 6.4 to 8.0% (46 to 64 mmol/mol) reduces microvascular disease morbidity. The ADVANCE trial showed that the absolute risk of major microvascular outcomes (worsening or new retinopathy or nephropathy) decreased by 1.5% (RR reduction 14%, CI 3% to 23%).[12] The VADT reported reduction in microalbuminuria with absolute risk reduction (ARR) of 2.5% (p=0.05).[14] The UKPDS 33 showed a 25% relative risk reduction in aggregate microvascular endpoints (95% CI 7% to 40%).[10] **1+**

A meta-analysis of individual participant data from ACCORD, ADVANCE, UKPDS, and VADT produced similar estimates: intensive glucose control compared with less-intensive glucose control (an absolute HbA1c reduction of 0.90% (95% CI 0.58 to 1.22) resulted in a relative reduction of 20% in the risk of renal events (HR 0.80, 95% CI 0.72 to 0.88) and in eye events of 13% (HR 0.87, 95% CI 0.76 to 1.00; p=0.04), but no reduction in neuropathy events (HR 0.98, 95% CI 0.87 to 1.09).[18] **1++**

3.5 HYPOGLYCAEMIA

Treatment to glycaemic targets increases incidence of hypoglycaemia. Significantly more episodes were reported in intensive versus conventional therapy groups in most studies, for example 10.5% *v* 3.5% for hypoglycaemia requiring medical assistance in the ACCORD trial (p<0.001),[13] 2.7% *v* 1.5% in the ADVANCE trial (HR 1.86, 95% CI 1.42 to 2.40).[12] UKPDS 33 showed a higher rate of major hypoglycaemia in participants on insulin or sulphonylureas than diet alone (insulin 1.8%, chlorpropamide 1.0%, glibenclamide 1.4%, diet 0.7%).[10] **1+**

3.6 WEIGHT GAIN

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

Table 1: Trials of intensive therapy to achieve glycaemic control

Trial (duration)	**Weight gain** (kg)	
	Intensive therapy group	**Conventional therapy group**
ACCORD[13] (3 years)	3.5	0.4
ADVANCE[12] (median 5 years)	0.0	-1.0
UKPDS 33[10] (median 10 years)	5.6	2.5
UKPDS 34[11] (median 10.7 years)	Not specified	
VADT[14] (median 5.6 years)	8.2	4.1

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

4 Metformin

Metformin is a small molecule from the biguanide family that has been used as a glucose-lowering agent for around 60 years. Actions at a molecular level are complex but effects on physiology include reduced production of glucose by the liver, weight loss or stabilisation, and improved insulin sensitivity. It is available in both standard- and modified-release forms.

4.1 GLYCAEMIC CONTROL

4.1.1 GLYCAEMIC CONTROL COMPARED TO PLACEBO (OR DIET)

One systematic review from 2005 considered the effectiveness of metformin monotherapy compared with placebo or any active combination.[19] When compared with placebo, metformin resulted in greater reduction of HbA1c (standardised mean difference, SMD 0.97, 95% CI -1.25 to -0.69), and fasting plasma glucose (FPG) (SMD -0.87, 95% CI -1.13 to -0.61), but there were no significant differences in BMI or weight, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, or blood pressure. **1++**

When compared with diet, there was greater reduction in HbA1c (SMD -1.06, 95% CI 1.89 to -0.22) and total cholesterol with metformin but no difference in FPG, BMI or weight, HDL cholesterol, LDL cholesterol, triglycerides, or blood pressure.

4.1.2 GLYCAEMIC CONTROL COMPARED WITH OTHER GLUCOSE-LOWERING AGENTS

The results of two large systematic reviews taken together suggest that metformin and second generation sulphonylureas have similar effects on HbA1c.[19,20] In the first, participants using metformin had marginally larger reductions in HbA1c compared with those using sulphonylureas (SMD -0.14, 95% CI -0.28 to -0.01).[19] In the second review, second generation sulphonylureas did not significantly lower HbA1c compared with metformin (SMD 0.09, 95% CI -0.30 to 0.10).[20] There was no significant difference in HbA1c between those participants using metformin and those using insulin, meglitinides or alpha-glucosidase inhibitors.[19] **1++**

An RCT in patients inadequately controlled by diet alone showed that canagliflozin was non-inferior to metformin with an HbA1c reduction of 1.42% standard error (SE) ±0.07 (15.5 mmol/mol ±0.8) with canagliflozin 300 mg and 1.37% ±0.07 (15 mmol/mol ±0.8) with canagliflozin 100 mg compared with 1.30% ±0.07 (14.2 mmol/mol ±0.8) with metformin monotherapy.[21] A similar study comparing metformin with dulaglutide in patients inadequately controlled by diet or a single oral agent showed that dulaglutide 1.5 mg was associated with greater mean HbA1c reduction (±SE) of -0.78% ±0.06 (-8.5 mmol/mol ±0.7) and -0.71% ±0.06 (-7.8 mmol/mol ±0.7) for 1.5 mg and 0.75 mg doses respectively compared with -0.56% ±0.06 (-6.1 mmol/mol ±0.7) in those using metformin.[22] A series of meta-analyses from AHRQ which incorporated 219 RCTs of glucose-lowering medications in people with type 2 diabetes reported only one statistically significant difference in HbA1c reduction when comparing any of the currently available drug classes when used as monotherapy. Metformin gave a greater reduction in HbA1c than DPP-4 inhibitors (pooled between-group difference -0.4% (-4.37 mmol/mol), 95% CI -0.5% to -0.3% (-5.46 to -3.28 mmol/mol)) in a meta-analysis of six short-duration (24–36 weeks) studies.[3] **1++** **1+**

4.2 HYPOGLYCAEMIA, WEIGHT GAIN AND ADVERSE EFFECTS

The main adverse event reported more frequently with metformin compared with placebo in one systematic review was diarrhoea (absolute risk increase (ARI) 6.8%; RR 3.09, 95% CI 1.58 to 6.07). Hypoglycaemia was reported more frequently with metformin compared with diet (ARI 2.9%; RR 4.21, 95% CI 1.40 to 12.66).[19] **1++**

Meta-analyses of RCTs of moderate to high quality involving comparisons of the effects of metformin, sulphonylurea and thiazolidinedione monotherapies on weight have favoured metformin by approximately -2.5 kg (pooled mean between-group differences). Comparisons with DPP-4 inhibitors showed a smaller benefit (-1.3 kg, 95% CI -1.6 kg to -1.0 kg).[3] One RCT showed that canagliflozin monotherapy was superior to metformin in terms of weight loss (difference from metformin 0.9 kg (-1.6 kg to -0.2 kg) for canagliflozin 100 mg; -1.8 kg (95% CI -2.4 kg to -1.1 kg) for canagliflozin 300 mg),[21] while another study showed comparable weight loss with metformin monotherapy compared with dulaglutide.[22] **1++** **1+**

A systematic review of the risk of lactic acidosis with metformin found no cases of fatal or non-fatal lactic acidosis in 274 comparative trials and cohort studies amounting to 59,321 patient-years of metformin use. It estimated that the upper limit of the true incidence of lactic acidosis per 100,000 patient years was 5.1 compared with 5.8 in the non-metformin group. Furthermore, there was no difference in lactate levels for metformin compared with non-metformin therapies.[23] **1++**

Metformin should be used with caution in people with moderate renal impairment, including progressive dose reductions in those with declining kidney function and avoided in those with severe renal impairment. Further information should be sought from the British National Formulary (BNF) and SPC.

4.3 CARDIOVASCULAR MORBIDITY AND MORTALITY

The UKPDS 34 allocated patients to either conventional (initial dietary modification with addition of a sulphonylurea when fasting plasma glucose >15 mmol/l or a more intensive glycaemic control strategy (which could include metformin, sulphonylurea or insulin therapy). For overweight patients (54% of whom were obese), those allocated to metformin (n=342) had improved outcomes compared with those on conventional treatment (n=411), for any diabetes-related outcomes (RR 0.68, 95% CI 0.58 to 0.87), diabetes-related death (RR 0.58, 95% CI 0.37 to 0.91) and all-cause mortality (RR 0.64, 95% CI 0.45 to 0.91).[11] The metformin group also had a significantly reduced risk of myocardial infarction (RR 0.61, 95% CI 0.41 to 0.89). There were no significant differences between metformin and other comparison arms for other outcomes such as stroke, peripheral arterial disease and microvascular disease. **1++**

Despite the benefits of metformin for overweight patients in comparison to a conventional treatment strategy, no benefits were observed for any of the above outcomes in comparisons between intensive treatment with metformin and intensive treatment with chlorpropamide, glibenclamide, or insulin (n=951).[11] **1++**

R **Metformin should be considered as the first-line oral treatment option for people with type 2 diabetes.**

5 Sulphonylureas

Sulphonylureas increase endogenous release of insulin from pancreatic β-cells. First-generation agents (acetohexamide, chlorpropamide, tolbutamide, tolazamide) are rarely used in the UK. Of the second-generation agents (glipizide, gliclazide, glibenclamide (glyburide), glimepiride) the most commonly used are gliclazide and glimepiride. Gliclazide is available in both standard and modified-release forms.

5.1 GLYCAEMIC CONTROL

UKPDS 33 showed that the sulphonylureas chlorpropamide and glibenclamide were more effective at reducing HbA1c than diet alone.[10] Placebo comparator studies with newer sulphonylureas showed reduction in HbA1c but these were largely short-duration trials of less than six months. One systematic review demonstrated a significant reduction in HbA1c with glibenclamide versus placebo.[24] **1+**

The results of two large systematic reviews taken together suggest that metformin and sulphonylureas have similar effects on HbA1c *(see section 4.1.2)*.[19,20] **1++**

Gliclazide MR and glimepiride were shown to be equally effective at reducing HbA1c at 27 weeks after initiation of treatment. HbA1c was not reduced further by glimepiride versus the longer established agent glibenclamide over 12–15 months.[25] **1+**

A meta-analysis of six short-term (16–52 weeks) studies including 1,364 patients suggested that sulphonylureas can achieve significant improvements in glycaemic control when added to metformin in patients who have inadequate glycaemic control.[26] **1++**

The NICE guideline on type 2 diabetes in adults recommends sulphonylureas as a second- or third-line treatment after metformin, or as an alternative first-line treatment in those who cannot tolerate or have contraindications to metformin.[4] The AHRQ review reported no significant difference in effect on HbA1c between sulphonylureas and metformin when used as monotherapy. There was insufficient evidence to compare sulphonylureas with thiazolidinediones (TZDs), DPP-4 inhibitors or glucagon-like peptide-1 (GLP-1) receptor agonists for long-term effects on HbA1c. Results of meta-analyses of trials comparing HbA1c reduction with sulphonylureas in combination with metformin versus other metformin-containing combinations did not favour sulphonylureas.[3] **1++ 4**

A number of trials have compared the use of sulphonylureas to newer diabetes treatments but most were designed to show a reduction in adverse effects rather than directly comparing HbA1c reduction (*see section 5.2*).

5.2 HYPOGLYCAEMIA, WEIGHT GAIN AND ADVERSE EFFECTS

The UKPDS 33 showed a higher rate of major hypoglycaemia (defined as requiring third-party help or medical intervention) and greater weight gain (2.6 kg for chlorpropamide, 1.7 kg for glibenclamide) in participants on sulphonylureas than in those on diet alone *(see sections 3.5 and 3.6)*.[27] A Scottish population-based study showed that one person with type 2 diabetes in every 100 treated with a sulphonylurea each year experienced an episode of major hypoglycaemia, compared with one in every 2,000 treated with metformin and one in every 10 treated with insulin.[28] One RCT over 27 weeks showed a significant reduction in confirmed hypoglycaemia (<3 mmol/l) with gliclazide MR versus glimepiride, while body weight increase was equivalent.[25] One systematic review reported that confirmed hypoglycaemia (defined as plasma glucose ≤3.3 mmol) was no more frequent compared with placebo in patients taking glipizide and glimepiride over three to four months although there was weight gain of 4.8 kg with glimepiride versus placebo.[24] **1+ 3**

The AHRQ review included 15 studies comparing the incidence of hypoglycaemia associated with use of sulphonylureas versus metformin. Five short-term RCTs were combined in meta-analysis, suggesting an increased risk of mild to moderate hypoglycaemia with sulphonylureas compared with metformin (pooled odds ratio (OR), 2.59, 95% CI 0.98 to 8.86). Nine studies were identified comparing TZDs with sulphonylureas of which five were combined in meta-analysis. The risk of total hypoglycaemia was higher in participants **1++**

taking sulphonylurea compared with TZD monotherapy (pooled OR 6.31, 95% CI 4.08 to 9.76). Four RCTs were identified comparing the incidence of hypoglycaemia in those taking sulphonylureas versus DPP-4 inhibitors. These could not be combined in meta-analysis but the odds of hypoglycaemia were significantly greater with sulphonylureas than DPP-4 inhibitors in all trials (range in OR 3.8 to 12.4). Five RCTs comparing sulphonylureas with GLP-1 receptor agonists for hypoglycaemia could also not be combined in meta-analysis but GLP-1 receptor agonists showed a lower incidence of mild, moderate and total hypoglycaemia in all trials (range in OR 3.1 to 5.3).[3] 1++

Given concerns about the risk of hypoglycaemia and weight gain with sulphonylureas, an RCT was conducted comparing alogliptin (25 mg) with glipizide (5 mg) once daily in older patients (aged 65–90 years) who had not achieved glycaemic targets on diet and exercise with or without a single oral agent as monotherapy.[29] In a post hoc analysis, the proportion of patients achieving the primary composite end point of HbA1c below 7.0% without hypoglycaemia or weight gain was significantly higher for the alogliptin group compared with the glipizide group (24% *v* 13%, p<0.03). Patients with a baseline HbA1c of <8.0% receiving alogliptin were also more likely to achieve HbA1c <7.0% without hypoglycaemia or weight gain than those receiving glipizide (OR 2.7, 95% CI 1.53 to 4.81).[30] 1-

An extension study to a 52-week double-blind RCT of once-daily canagliflozin 100 mg, canagliflozin 300 mg or glimepiride in addition to metformin monotherapy followed up participants to 104 weeks. Post hoc analysis showed that the proportion of participants achieving reductions in both HbA1c and body weight at 104 weeks was 66%, 71%, and 27%, respectively. Odds for achieving this composite end point favoured canagliflozin 100 and 300 mg compared with glimepiride (OR 5.6, 95% CI 4.2 to 7.5 and 7.4, 95% CI 5.5 to 9.8, respectively).[31] 1++

A similar extension study of an RCT comparing once-daily saxagliptin 5 mg with glipizide (5–20 mg/day, titrated) on a background of metformin monotherapy indicated lower rates of all types of hypoglycaemia (including severe) with saxagliptin over 104 weeks: 38.4% in the glipizide group versus 3.5% in the saxagliptin group experienced any hypoglycaemia (between-group difference -34.9%, 95% CI -39.8% to -30.0%).[32] Fewer than 3% of all hypoglycaemia events were nocturnal, but all of these occurred in those taking glipizide rather than saxagliptin.[33] 1++

In one RCT of exenatide twice daily or glimepiride in individuals who had not achieved adequate glycaemic control on metformin over three years, body weight decreased with exenatide (-3.9 kg, SE 0.33) and increased with glimepiride (1.3 kg, SE 0.32, p<0.0001) while documented symptomatic hypoglycaemia (blood glucose <3.9 mmol/L) was reported by 98 (19.2%) with exenatide and 237 (46.7%) with glimepiride, respectively (p<0.0001).[34] 1-

Sulphonylureas should be used with caution in people with mild/moderate renal impairment and avoided in those with severe renal impairment. Further information should be sought from the BNF and SPC.

5.3 CARDIOVASCULAR MORBIDITY AND MORTALITY

The AHRQ review identified two high-quality RCTs and three retrospective cohort studies comparing metformin with sulphonylureas.[3] The first RCT, A Diabetes Outcome Progression trial (ADOPT) reported a numerically but not significantly higher incidence of fatal myocardial infarction (MI) with glibenclamide (3/1,441, 0.2%) than metformin (2/1,454, 0.1%) (RR 1.5, 95% CI 0.3 to 9.0), but lower rates of cardiovascular disease (CVD) adverse events over four years follow up with glibenclamide (26/1,441, 1.8%) than with metformin (46/1,454, 3.2%). However, although 4,360 individuals were randomised, absolute event rates were very low and the study was not designed to examine cardiovascular disease and therefore had insufficient statistical power for this outcome. The second RCT was conducted in China among patients with known coronary heart disease and randomised 304 participants to glipizide (30 mg daily) or metformin (1.5 g daily) for five years (median follow up). While the hazard ratio for the primary composite cardiovascular outcome (non-fatal myocardial infarction, non-fatal stroke or arterial revascularisation, death from a cardiovascular cause, and death from any cause) for metformin treatment was 0.54 (95% CI 0.30 to 0.90, p=0.026), there was no statistically significant difference in the rate of cardiovascular mortality with glipizide (11/148, 7.4%) compared with metformin (7/156, 4.5%) (RR of cardiovascular mortality comparing sulphonylurea with metformin 1.66 (95% CI 0.66 to 4.16). 1++

All three cohort studies reported a significantly higher risk of cardiovascular mortality for sulphonylurea versus metformin.[3]

In overweight participants of UKPDS 34 *(see sections 3 and 4.3)* non-statistically significant trends were observed for higher rates of diabetes-related death, all-cause mortality, myocardial infarction and stroke with an intensive treatment strategy based on sulphonylureas or insulin than with an intensive treatment strategy based on metformin.[11] However, in comparisons of intensive treatment strategies versus conventional treatment with agents used for the seven major UKPDS outcomes, the only mean relative risk higher than unity was for stroke when treatment was based on sulphonylureas or insulin (RR 1.14, 95% CI 0.70 to 1.84, not statistically significant). **1++**

An ongoing large RCT (CAROLINA) will provide comparative evidence on the cardiovascular safety of glimepiride in relation to linagliptin.[35,36]

R **Sulphonylureas should be considered as first-line oral agents in people who are intolerant of, or have contraindications to metformin.**

R **Sulphonylureas should be considered as add-on second-line treatment to other oral therapies and may be useful in triple oral therapy.**

✓ Sulphonylurea therapy is associated with hypoglycaemia (caution should be taken in the elderly) and weight gain.

6 Thiazolidinediones

Thiazolidinediones increase whole-body insulin sensitivity by activating nuclear receptors and promoting esterification and storage of circulating free fatty acids in subcutaneous adipose tissue. Pioglitazone is now the only TZD with a marketing authorisation in the UK.

6.1 PIOGLITAZONE

6.1.1 GLYCAEMIC CONTROL

Pioglitazone is effective at lowering HbA1c as monotherapy and in dual or triple therapy when combined with metformin, sulphonylureas, DPP-4 inhibitors or insulin.[3,29,37,38] Combination therapy using doses of 15–30 mg daily have been shown to lower HbA1c by 0.64 to 1.26% (6.99 to 13.77 mmol/mol).[39] **1++**

Some sodium glucose co-transporter 2 (SGLT2) inhibitors, DPP-4 inhibitors and GLP-1 receptor agonists are licensed for use with pioglitazone, but specific evidence was not identified in support of all combinations.

Pioglitazone is accepted for restricted use by SMC as monotherapy for individuals who have already experienced severe hypoglycaemia or in whom metformin and sulphonylureas are contraindicated or not tolerated. It is not accepted as monotherapy for any other group.

6.1.2 HYPOGLYCAEMIA, WEIGHT GAIN AND ADVERSE EFFECTS

A systematic review of 18 RCTs with 11,565 participants providing loosely defined data on oedema reported a raised incidence with pioglitazone (RR 2.86, 95% CI 2.14 to 3.18).[40] This finding has been supported by other meta-analyses.[39,41-43] **1++**

Pioglitazone is associated with weight gain.[39] Meta-analyses of RCTs have shown TZDs to increase weight more than sulphonylureas (mean difference 1.2 kg, 95% CI 0.6 to 1.8 kg), DPP-4 inhibitors (range in mean difference 2.3–2.5 kg) and GLP-1 receptor agonists (mean difference 3.5 kg, data not pooled).[3] Thiazolidinediones reduced weight less than metformin (mean difference 2.6 kg, 95% CI 1.2 to 4.1 kg).[44] **1++**

One meta-analysis of five RCTs of one to four years duration reported fractures in 5.8% of women with type 2 diabetes treated with TZDs in comparison with 3.0% treated with other agents (OR 2.23, 95% CI 1.65 to 3.01). In this meta-analysis there was no increase in rates of fracture in men (OR 1.00, 95% CI 0.73 to 1.39).[45] However, nationwide Scottish epidemiological data showed that, in 37,479 individuals exposed to TZDs, hip fracture risk increased with cumulative exposure in both men (OR 1.20, 95% CI 1.03 to 1.41) and women (OR 1.18, 95% CI 1.07 to 1.29).[46] Similarly, a prospective population-based cohort study confirmed a 28% increased risk of peripheral fracture in both men and women (HR 1.28, 95% CI 1.10 to 1.48).[47] **1++ 2+ 3**

A meta-analysis of 14 epidemiological studies reported an increased risk of bladder cancer in people who had ever used pioglitazone compared with those who had never used it (HR 1.16, 95% CI 1.06 to 1.25), with a small incremental risk associated with each year of treatment (HR 1.16, 95% CI 1.03 to 1.30) or 10 gram increase in cumulative dose (HR 1.05, 95% CI 1.02 to 1.09).[48] **2+**

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA)[49] advise that this agent should not be used in patients with active bladder cancer or a history of bladder cancer. Pioglitazone should not be used in patients with hepatic impairment. Further information should be sought from the BNF and SPC.

6.1.3 CARDIOVASCULAR MORBIDITY

A Cochrane systematic review reported insufficient evidence to draw conclusions on the effect of pioglitazone on outcomes such as mortality, morbidity, adverse events or health-related quality of life.[40] **1++**

A subgroup analysis from the PROactive trial suggested a reduction in fatal and non-fatal MI in the subgroup with previous myocardial infarction (n=2,445, HR 0.72, 95% CI 0.52 to 0.99, p=0.045; number needed to treat (NNT)=51 (95% CI 26 to 2,634).[50] In patients with previous stroke (n=984), subgroup analysis showed that **1+**

pioglitazone reduced fatal or non-fatal stroke (HR 0.53, 95% CI 0.34 to 0.85, p=0.0085; NNT=21, 95% CI 12 to 75), while there was no effect on stroke risk in patients with no history of prior stroke (HR 1.06, 95% CI 0.73 to 1.52, p=0.767).[51] | 1+

However, a meta-analysis of 84 published and 10 unpublished trials of pioglitazone compared with placebo or other therapy, and excluding the PROactive trial, reported a reduction in all-cause mortality with pioglitazone (OR 0.30, 95% CI 0.14 to 0.63), but no significant effect on non-fatal coronary events.[52] A further meta-analysis with 16,390 patients found a reduction in the primary composite endpoint (death, MI or stroke) with pioglitazone compared with control (HR 0.82, 95% CI 0.72 to 0.94, p=0.005).[53] | 1++ 1-

A meta-analysis of studies including chronic heart failure (CHF) as an end point found an increased risk of CHF with pioglitazone when compared with placebo or other medications, with an overall RR of 1.32 (95% CI 1.04 to 1.68).[43] | 1+

These findings are corroborated by further data from a manufacturer-sponsored meta-analysis including 16,390 patients.[53] Serious heart failure was increased with pioglitazone (200 patients (2.3%) *v* 139 patients in the control group (1.8%) (HR 1.41, 95% CI 1.14 to 1.76, p=0.002)). | 1-

The PROactive study found that, although more patients treated with pioglitazone had a serious heart failure event compared with placebo (p=0.007), mortality due to heart failure was similar.[54] | 1-

A study comparing pioglitazone to glibenclamide in patients with known grade II or III New York Heart Association (NYHA) heart failure functional class reported more hospitalisations with pioglitazone (9.9%) than glibenclamide (4.7%) but no difference in mortality.[55] | 1+

R **Pioglitazone should be considered, usually as dual or triple therapy, for lowering HbA1c.**

R **Pioglitazone should not be used in patients with heart failure.**

R **The risk of fracture should be considered during long-term use of pioglitazone.**

✓ Patients prescribed pioglitazone should be made aware of the increased risk of peripheral oedema, heart failure, weight gain, bladder cancer and fractures.

6.2 ROSIGLITAZONE

In September 2010 the European Medicines Agency (EMA) completed a review of rosiglitazone-containing medicines at the request of the European Commission, following reports of an increase in the risk of cardiovascular problems with rosiglitazone. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of rosiglitazone did not outweigh its risks, and that the marketing authorisation for all rosiglitazone-containing medicines should be suspended across the European Union (EU). The marketing authorisation for Avandia (rosiglitazone) in the EU was suspended on 11 July 2015 when the holder of the MA decided not to apply for a renewal. Further information can be found on the EMA website (www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2016/06/WC500208350.pdf).

In February 2011 the U.S. Food and Drug Administration (FDA) notified the public that information on the cardiovascular risks of rosiglitazone has been added to the physician labelling and patient Medication Guide. Following re-evaluation of contemporary evidence on the cardiovascular safety of rosiglitazone, restrictions on its use were reduced in 2013 and, ultimately, removed in 2015. From December 2015, distribution of rosiglitazone-containing medicines is no longer restricted in the USA. Further details are available on the FDA website (www.fda.gov/Drugs/DrugSafety/ucm376389.htm).

7 Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 inhibitors are oral agents that inhibit the activity of the enzyme DPP-4 and hence prolong the actions of endogenous GLP-1 (*see section 9*). Five DPP-4 inhibitors are currently available: alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin.

7.1 GLYCAEMIC CONTROL

Compared with placebo, sitagliptin, vildagliptin and saxagliptin were shown to be effective at lowering HbA1c by 0.7% (7.65 mmol/mol), 0.6% (6.56 mmol/mol) and 0.6% (6.56 mmol/mol) respectively.[56-58] These data include studies where DPP-4 inhibitors have been used as monotherapy compared with placebo,[56-58] dual therapy in combination with metformin, sulphonylurea or TZD compared with placebo[56-58] and for sitagliptin as triple therapy in combination with metformin and sulphonylurea.[59] The AHRQ review showed greater reduction in HbA1c with metformin than DPP-4 inhibitors (pooled mean between-group difference -0.4% (-4.37 mmol/mol), 95% CI -0.5% to -0.3% (-5.46 to -3.28 mmol/mol)) and greater reduction with sulphonylureas than DPP-4 inhibitors (pooled mean between-group difference -0.2% (-2.19 mmol/mol), 95% CI, -0.3 to -0.1% (-3.3 to -1.09 mmol/mol)).[3] However, there is some evidence from a network meta-analysis of the benefit of DPP-4 inhibitors over metformin after two years of treatment (mean relative difference in HbA1c between vildagliptin and metformin 0.5% (-5.46 mmol/mol) (95% credible interval -0.78 to -0.22% (8.52 to -2.40 mmol/mol)).[4] **1++ 4**

Linagliptin, sitagliptin and vildagliptin are accepted for use as monotherapy by SMC. They should be considered for use in those for whom both metformin and sulphonylureas are inappropriate due to contraindications or intolerance.

The AHRQ review reported that in combination therapy, metformin and a DPP-4 inhibitor provide HbA1c reduction that is:

i. greater than metformin alone (pooled between-group difference -0.65% (-7.10 mmol/mol), 95% CI -0.60% to -0.70% (-6.56 to -7.65 mmol/mol));
ii. not significantly different to metformin and a sulphonylurea (pooled between-group difference -0.09% (-0.98 mmol/mol), 95% CI -0.21% to 0.03% (-2.30 to 0.33 mmol/mol));
iii. less than metformin in combination with either a TZD (pooled between-group difference 0.12% (1.31 mmol/mol), 95% CI 0.02% to 0.21% (0.22 to 2.30 mmol/mol)), an SGLT2 inhibitor (pooled between-group difference 0.17% (1.86 mmol/mol), 95% CI 0.08% to 0.26% (0.87 to 2.84 mmol/mol)) or a GLP-1 agonist (pooled between-group difference 0.65% (7.10 mmol/mol), 95% CI 0.54% to 0.75% (5.90 to 8.20 mmol/mol)). **1++**

The authors note that their meta-analyses may have underestimated the magnitude of HbA1c reduction with the metformin and TZD combination with respect to the metformin and DPP-4 inhibitor combination as some studies did not use optimal doses of metformin plus TZD.[3]

The combination of metformin, sitagliptin and a sulphonylurea is not as effective as metformin and neutral protamine Hagedorn (NPH) insulin for HbA1c reduction (mean difference between groups 2.10% (22.95 mmol/mol), 95% credible interval 0.80% to 3.45% (8.74 to 33.71 mmol/mol)) and compares poorly with all other insulin-containing regimens.[4] **4**

When added to combination therapy of metformin and a sulphonylurea, sitagliptin provided less HbA1c reduction at 52 weeks than the SGLT2 inhibitor canagliflozin. The latter also reduced weight and lowered blood pressure.[60] **1++**

The addition of linagliptin to basal insulin and metformin combination therapy produced a significant reduction in HbA1c at 24 weeks compared with placebo (-0.7% (-7.65 mmol/mol), 95% CI 0.8 to 0.6% (-8.74 to -6.56 mmol/mol), with similar rates of investigator-reported hypoglycaemia in each group (30.7 *v* 31.6%).[61] Similarly, pretreatment with sitagliptin prior to commencing basal insulin glargine U100 (100 units/ml) provided superior glycaemic control despite lower insulin doses and fewer episodes of hypoglycaemia.[62] **1+**

7.2 HYPOGLYCAEMIA, WEIGHT GAIN AND ADVERSE EFFECTS

Systematic reviews indicate that DPP-4 inhibitors are well tolerated with no difference in discontinuation rates due to adverse events between sitagliptin or vildagliptin intervention and placebo or active control groups.[57,63] In the AHRQ review, data from six RCTs showed lower rates of symptomatic hypoglycaemia in participants taking DPP-4 inhibitors compared with metformin (pooled OR 0.52, 95% CI 0.30 to 0.90). Three short-term studies comparing TZDs with DPP-4 inhibitors that could not be combined in meta-analysis showed no significant differences in overall hypoglycaemia. Four RCTs of varying duration showed lower rates of hypoglycaemia with DPP-4 inhibitors compared with sulphonylureas (range in OR 3.8 to 12.4) while a single RCT comparing DPP-4 inhibitors with SGLT2 inhibitors reported no significant difference in hypoglycaemia between groups. In a further trial comparing a DPP-4 inhibitor (sitagliptin) with a GLP-1 receptor agonist (exenatide), rates of symptomatic hypoglycaemia were low with both agents (3.1% *v* 5.2%, respectively).[3] **1++**

The pooled OR for mild or moderate hypoglycaemia across 27 RCTs comparing metformin and a DPP-4 inhibitor combination therapy with metformin monotherapy indicated a similar risk of hypoglycaemia (pooled OR 0.97, 95% CI 0.63 to 1.51).[3] DPP-4 inhibitors in combination with metformin were associated with lower rates of hypoglycaemia than either sulphonylureas or basal insulin in combination with metformin. All other metformin-based combinations resulted in similar rates of hypoglycaemia to metformin and a DPP-4. **1++**

In the AHRQ review, six RCTs reported smaller reductions in weight with DPP-4 inhibitors than metformin (pooled between-group difference 1.3 kg, 95% CI 1.0 kg to 1.6 kg). One double-blind RCT comparing the DPP-4 inhibitor, sitagliptin (100 mg daily), with the SGLT2 inhibitor, empagliflozin (10 mg and 25 mg daily) found greater weight loss with empagliflozin (calculated mean between-group difference of 2.5 kg and 2.7 kg for 10 mg and 25 mg empagliflozin, respectively). However, two RCTs found that use of DPP-4 inhibitors resulted in greater weight loss than TZDs (mean between-group difference of 2.3 kg and 2.5 kg. This was also the case for three RCTs which found that use of DPP-4 inhibitors resulted in greater weight loss than sulphonylureas (range in mean between-group differences of 0.9 kg to 1.8 kg).[3] **1++**

In keeping with these findings, weight gain was lower when metformin was combined with a DPP-4 inhibitor than with a TZD or a sulphonylurea. However, greater weight loss was observed with GLP-1 receptor agonists than with DPP-4 inhibitors when both were combined with metformin.[3]

Cases of pancreatitis were numerically (but not statistically) higher with DPP-4 inhibitors than with placebo in the large SAVOR-TIMI 53,[64] EXAMINE[65] and TECOS[66] trials There is also low-quality evidence from four RCTs that severe allergic reactions are more prevalent with DPP-4 inhibitors when added to metformin compared with metformin alone (range of between-group rate differences for severe allergic reaction 0.4% to 1.1%),[3] however, such reactions are uncommon. **1+** **1++**

Dose reductions are advised for specific DPP-4 inhibitors (alogliptin, sitagliptin, saxagliptin and vildagliptin) when used in people with moderate/severe renal impairment. Further information should be sought from the BNF and SPC.

7.3 CARDIOVASCULAR MORBIDITY AND MORTALITY

Three major cardiovascular (CV) outcome trials of DPP-4 inhibitors compared with placebo and standard of care have been conducted to date (SAVOR-TIMI 53,[64] EXAMINE[65] and TECOS[66]). An ongoing study (CARMELINA) is investigating the long-term impact on cardiovascular morbidity, mortality and renal function of treatment with linagliptin in individuals at high risk of cardiovascular disease.[67]

All three completed trials met their predefined criteria for non-inferiority of DPP-4 inhibitors for the composite end point of cardiovascular death, myocardial infarction, or ischaemic stroke in patients at high risk for cardiovascular events. A limitation of their design was heterogeneity of comparator treatments. There was an increase in the rate of hospitalisation for heart failure over two years with saxagliptin compared with placebo in SAVOR-TIMI 53 (3.5% *v* 2.8%; HR 1.27, 95% CI 1.07 to 1.51, p=0.007)[64] and there was a numerically (but not statistically significant) small excess of heart failure over 18 months with alogliptin versus placebo in the EXAMINE trial.[68] In contrast, rates of hospitalisation for heart failure were almost identical with sitagliptin versus placebo over three years in the TECOS study (HR 1.00, 95% CI 0.83 to 1.20, p=0.98).[66] 1^{+} 1^{++}

R **DPP-4 inhibitors should be considered, usually as dual or triple therapy, for lowering HbA1c.**

8 Sodium glucose co-transporter 2 inhibitors

Sodium glucose co-transporter 2 (SGLT2) inhibitors reduce renal glucose re-absorption resulting in increased glucose excretion equivalent to a net loss of 200–300 kcal/day. Their glucose-lowering effect is therefore independent of pancreatic β-cell function. Three drugs are currently licensed in this class; canagliflozin, dapagliflozin and empagliflozin.

8.1 GLYCAEMIC CONTROL

8.1.1 MONOTHERAPY

A technology appraisal of SGLT2 inhibitors as monotherapy identified three RCTs of daily treatment with dapagliflozin 10 mg.[69] Dapagliflozin reduced HbA1c by 0.39% (4.26 mmol/mol), 0.66% (7.21 mmol/mol) and 0.82% (8.96 mmol/mol) more than placebo from baseline HbA1c of 7.50–8.35% (58.47–67.76 mmol/mol) for participants taking placebo and 7.46–8.28% (58.03–66.99 mmol/mol) for those taking dapagliflozin. The reduction was greater in individuals with a higher baseline HbA1c. In two placebo-controlled RCTs of canagliflozin 100 mg daily, HbA1c was reduced by 0.91% (9.95 mmol/mol) and 1.01% (11.04 mmol/mol), from an initial baseline of 8.0% (63.93 mmol/mol). In one RCT treatment with 300 mg canagliflozin reduced HbA1c by 1.17% (12.79 mmol/mol) compared with placebo. In two RCTs, compared with placebo, empagliflozin 10 mg reduced HbA1c by 0.74% (8.09 mmol/mol) while empagliflozin 25 mg reduced it by 0.86% (9.40 mmol/mol); baseline HbA1c was 7.91% (62.95 mmol/mol) for participants taking placebo and 7.87–7.99% (62.51–63.83 mmol/mol) for those taking empagliflozin. **1++**

When combined in network meta-analysis, pooled results for all comparisons with placebo were consistent with those from the technology appraisal.[4] **4**

Based on low-quality evidence, the AHRQ review reported no significant difference in HbA1c reduction between metformin and SGLT2 inhibitor monotherapy. There was insufficient evidence available for comparisons with all other monotherapy agents.[3]

One RCT randomised participants to receive empagliflozin 10 mg, empagliflozin 25 mg, placebo, or sitagliptin 100 mg once daily for 24 weeks. At extended follow up after 76 weeks, adjusted mean changes from baseline in HbA1c were -0.78% (-8.52 mmol/mol) (95% CI -0.94 to 0.63 (-10.27 to -6.89 mmol/mol), p <0.001) and -0.89% (-9.73 mmol/mol) (95% CI -1.04 to -0.73 (-11.73 to -8.09 mmol/mol), p <0.001) for empagliflozin 10 mg and 25 mg, respectively, compared with placebo, Compared with sitagliptin, adjusted mean changes from baseline in HbA1c at week 76 were greater for empagliflozin 25 mg (differences of adjusted means -0.22% (-2.40 mmol/mol), 95% CI -0.38 to -0.07 (-4.15 to 0.77 mmol/mol), p=0.005), but not for empagliflozin 10 mg (differences of adjusted means 0.12% (-1.31 mmol/mol), 95% CI -0.28 to 0.04 (-3.06 to 0.44 mmol/mol), p=0.131).[70] **1+**

Based on a NICE technology appraisal, canagliflozin, dapagliflozin and empagliflozin monotherapies are accepted as options for treating type 2 diabetes in adults for whom metformin is contraindicated or not tolerated and when diet and exercise alone do not provide adequate glycaemic control, only if:

- a DPP-4 inhibitor would otherwise be prescribed, and
- a sulphonylurea or pioglitazone is not appropriate.[71]

8.1.2 COMBINATION THERAPY

The combination of metformin with an SGLT2 inhibitor was more effective at lowering HbA1c compared with metformin alone (nine trials; pooled between-group difference in HbA1c, -0.61% (-6.67 mmol/mol), (95% CI -0.71 to -0.52% (-5.68 to -7.76 mmol/mol)), metformin and sulphonylurea (three trials; pooled between-group difference in HbA1c of 0.17% (-1.86 mmol/mol), (95% CI -0.20 to -0.14% (-2.19 to -1.53 mmol/mol)) or metformin and DPP-4 inhibitor (four trials; pooled between-group difference in HbA1c, 0.17% (-1.86 mmol/mol) (95% CI -0.26 to -0.08% (-2.62 to -0.87 mmol/mol)).[3] **1++**

Three RCTs were identified which compared SGLT2 inhibitors with sitagliptin when added to other glucose-lowering agents. The first found that a higher proportion of patients treated with canagliflozin than with sitagliptin achieved an HbA1c at week 52 of less than 7.0% (47.6% *v* 35.3%; OR 1.79, 95% CI 1.30 to 2.47) or 8.0% (64 mmol/mol) (85.0% *v* 66.0%; OR 3.31, 95% CI 2.26 to 4.86) when added to metformin and a sulphonylurea. A lower proportion also had an HbA1c over 9% (75 mmol/mol) (1.9% *v* 8.5%; OR 0.18, 95% CI 0.08 to 0.43).[60] **1++**

The second trial demonstrated that, when added to metformin over 52 weeks, canagliflozin 100 mg demonstrated non-inferiority and canagliflozin 300 mg demonstrated statistical superiority to sitagliptin in lowering HbA1c (mean changes 0%, 95% CI -0.12 to 0.12 (-1.31 to 1.31 mmol/mol) and 0.15% (-1.65 mmol/mol), 95% CI -0.27 to -0.03 (-2.95 to -0.33 mmol/mol), respectively).[72] **1++**

The third trial found that when added to sitagliptin, dapagliflozin significantly reduced mean HbA1c levels versus placebo after 24 weeks (placebo-corrected change -0.5% (-5.2 mmol/mol), 95% CI 0.6 to -0.3% (-6.8 to -3.7 mmol/mol)).[73] **1+**

Several RCTs have compared SGLT2 inhibitors with placebo in people receiving background insulin.[74-77] In an extension study over two years, the mean HbA1c change from baseline at 104 weeks in participants randomised to dapagliflozin added on to insulin was 0.32% (-3.50 mmol/mol) (95% CI 0.48 to -0.16% (-5.25 to -1.75 mmol/mol)) in the 2.5 mg dapagliflozin group and 0.53% (5.79 mmol/mol) (95% CI -0.70 to -0.37% (-7.65 to -4.04 mmol/mol) in the 10 mg dapagliflozin group) compared with placebo added to insulin.[76] **1++**

In an extension study over 52 weeks, more than 50% of patients randomised to either dapagliflozin or placebo were on background insulin treatment, on its own or in combination with another oral hypoglycaemic agent. The placebo-corrected reduction in HbA1c was significant at week 24 (0.46%, (5.03 mmol/mol), p<0.0001) and maintained at week 52 (0.66%, (-7.21 mmol/mol)).[74] Another RCT over 52 weeks showed reductions in HbA1c with canagliflozin 100 and 300 mg compared with placebo of -0.58% (-6.3 mmol/mol) (95% CI -0.68 to -0.48 (-7.4 to -5.2 mmol/mol)) and 0.73% (-8.0 mmol/mol) (95% CI -0.83 to 0.63 (-9.1 to -6.9 mmol/mol)), respectively.[75] **1++**

8.2 HYPOGLYCAEMIA, WEIGHT GAIN AND ADVERSE EFFECTS

As SGLT2 inhibitors mediate their effects independently of insulin, there is a low risk of hypoglycaemia with their use. The incidence of hypoglycaemia associated with SGLT2 inhibitor monotherapy and combination therapy has been tested in a series of meta-analyses.

A meta-analysis of four short-term RCTs (≤24 weeks) reported that there was no statistically significant difference in the odds of any hypoglycaemia between metformin and SGLT2 inhibitor monotherapy. Confidence intervals were wide for all included results due to the very small number of events reported. Similarly, meta-analysis of seven short-term RCTs (≤24 weeks) demonstrated a weighted pooled odds ratio for the combination of metformin plus an SGLT2 inhibitor compared with metformin monotherapy of 1.74 (95% CI 0.83 to 3.66).[3] **1++**

A meta-analysis of three RCTs found a lower rate of mild or total hypoglycaemia with the combination of metformin plus an SGLT2 inhibitor rather than metformin plus a sulphonylurea (OR 0.08, 95% CI 0.03 to 0.17).[3] **1++**

A meta-analysis of five RCTs (12 to 78 weeks) showed no difference in the rate of total hypoglycaemia between individuals randomised to metformin plus a SGLT2 inhibitor or to metformin plus a DPP-4 inhibitor (OR 0.98, 95% CI 0.06 to 15.84).[3] **1++**

Two RCTs have reported a greater incidence of hypoglycaemia with canagliflozin than placebo when used in combination with insulin. One RCT found that more individuals treated with canagliflozin 100 and 300 mg than with placebo had one or more documented hypoglycaemic episodes (33.8%, 36.5% and 17.9%, respectively) over 52 weeks of treatment.[78] In a further trial, rates of documented hypoglycaemia were numerically, but not statistically, higher in those receiving canagliflozin 300 or 100 mg than placebo (57%, 59% and 48%, respectively).[75] **1++**

The AHRQ review reported that SGLT2 inhibitors are associated with a greater reduction in weight compared with metformin (-1.3 to -1.4 kg; three trials) or DPP-4 inhibitors (-2.5 to 2.7 kg; one trial) when used as monotherapy. Compared with metformin monotherapy, the combination of metformin plus an SGLT2 inhibitor had a greater weight reduction (2.0 kg, 95% CI -1.5 to -2.5 kg; seven trials). Compared with the combination of metformin plus a sulphonylurea the combination of metformin plus an SLGT-2 inhibitor had a more favourable effect on weight (pooled mean between-group differences in weight 4.7 kg, 95% CI, 4.4 kg to 5.0 kg; three trials). The combination of an SGLT2 inhibitor with metformin was associated with a greater reduction in body weight when compared with metformin plus a DPP-4 inhibitor (range in mean between-group differences in weight of 1.8 kg to 3.6 kg).[3] 1++

Point estimates and credible intervals from a NICE technology appraisal of SGLT2 inhibitors as monotherapy compared with placebo (using direct and indirect comparisons) were consistent with these findings.[69] 1++

A reduction in body weight was also seen in studies comparing SGLT2 inhibitors with placebo in patients on insulin therapy. One RCT demonstrated a reduction in body weight of 0.9 to 1.4 kg in patients treated with dapagliflozin compared with an increase in weight of 1.8 kg in the placebo group at 104 weeks.[76] A further RCT reported a reduction of -1.9 to 3.5 kg in mean body weight of individuals treated with canagliflozin over 52 weeks compared with placebo.[75] 1++

The most commonly reported adverse event with this class of drugs is genital mycotic infections. A meta-analysis of three medium- to high-quality, short duration RCTs compared metformin with SGLT2 inhibitors and found more genital infections in those allocated to SGLT2 inhibitors (pooled OR, 4.1, 95% CI, 2.0 to 8.3). The same meta-analysis compared outcomes from use of 100 mg sitagliptin daily versus an SGLT2 inhibitor in two trials. Both reported higher numerical rates of genital infections among both women and men with SGLT2 inhibitors compared with sitagliptin, with some of the comparisons statistically significant. In all comparisons involving SGLT2 inhibitors used as combination therapy the comparator showed a lower incidence of genital mycotic infections.[3] 1++

There have been reports of diabetic ketoacidosis (DKA) associated with the use of SGLT2 inhibitors. The EMA published a review in February 2016 and recommended that the product information be updated to list DKA as a rare adverse reaction (affecting up to 1 in 1,000 patients).[79] SGLT2 inhibitors should therefore be used with caution in patients at risk of DKA, particularly those with low endogenous insulin secretion, increased insulin requirement (due to illness, surgery or alcohol misuse) or conditions that result in reduced oral intake or severe dehydration. SGLT2 inhibitors should be stopped temporarily if a patient is undergoing major surgery or during serious illness.

An approximately twofold increase in lower limb amputations in canagliflozin-treated participants compared with those taking placebo was seen in the CANagliflozin cardioVascular Assessment Study (CANVAS) and CANVAS-R trials. The EMA triggered an assessment of the balance of benefits and harms across SGLT2 inhibitors with respect to possible risk of amputations and, having considered all of the available evidence, concluded that the benefit-risk balance of SGLT2 inhibitors remained positive but recommended that the product information of all authorised SGLT2 inhibitors should contain information on the risk of lower limb amputation.[80]

Canagliflozin was associated with a higher rate of all fractures compared with placebo in the CANVAS trial (15.4 *v*. 11.9 participants with fracture per 1,000 patient-years; HR 1.26, 95% CI, 1.04 to 1.52).[81] This association was not seen in CANVAS-R. The risk of fractures and effects on bone mineral density are under evaluation and the FDA advise consideration of all of the factors associated with fracture risk when prescribing canagliflozin. 1++

According to current licensing, SGLT2 inhibitors should not be initiated in individuals with an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2. At levels below this, dose reductions are advised according to individual agents. Further information should be sought from the BNF and SPC.

8.3 CARDIOVASCULAR MORBIDITY AND MORTALITY

Two trials of SGLT2 inhibitors with CV outcomes (EMPA-REG and CANVAS) have published results. Several others are ongoing including CREDENCE[82] and DECLARE-TIMI 58.[83]

There is currently insufficient RCT evidence on the cardiovascular mortality and morbidity of SGLT2 inhibitors to combine in meta-analysis.[3] **1++**

The EMPA-REG trial was a double-blind RCT that investigated CV outcomes in patients with type 2 diabetes at high risk of CVD treated with empagliflozin (n=7,020). Over 99% of participants had established CV disease, with 76% having coronary artery disease. Participants received empagliflozin (10 or 25 mg) or placebo with continuation of standard of care management for diabetes and comorbid conditions. The primary outcome, a composite of cardiovascular mortality, non-fatal MI and non-fatal stroke occurred at a significantly lower rate in participants on empagliflozin than in those taking placebo (10.5 *v* 12.1%) (HR 0.86, 95% CI 0.74 to 0.99; p<0.001 for non-inferiority and p=0.04 for superiority). Empagliflozin also resulted in a significantly lower risk of death from cardiovascular causes (ARR 2.2%; HR 0.62, 95% CI 0.49 to 0.77), death from any cause (ARR 2.6%; HR 0.68, 95% CI 0.57 to 0.82) and hospitalisation for heart failure (ARR 1.4%; HR 0.65, 95% CI 0.50 to 0.85) compared with placebo.[84] **1+**

In the same trial there was a significant reduction in a composite renal outcome of progression to microalbuminuria, doubling of serum creatinine, initiation of renal replacement therapy or death with empagliflozin.[85] **1+**

The CANVAS trial examined the effects of canagliflozin in patients with type 2 diabetes and high CV risk. The rate of the primary outcome (death from CV causes, non-fatal heart attack and non-fatal stroke) was lower with canagliflozin than with placebo (26.9 *v* 31.5 participants per 1,000 patient-years, HR 0.86 (95% CI 0.75 to 0.97); p<0.001 for non-inferiority; p=0.02 for superiority).[81] **1++**

There was also a lower rate of progression of albuminuria in patients treated with canagliflozin compared with placebo (89.4 *v* 128.7 participants with an event per 1,000 patient-years, HR 0.73, 95% CI, 0.67 to 0.79) as well a reduction in the need for renal replacement therapy or death from renal causes.

R **SGLT2 inhibitors should be considered as an add-on therapy to metformin in people with type 2 diabetes.**

R **In individuals with type 2 diabetes and established cardiovascular disease, SGLT2 inhibitors with proven cardiovascular benefit** (currently empagliflozin and canagliflozin) **should be considered.**

9 Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide (GLP)-1 is one of the key 'incretin' hormones. These are a group of rapidly metabolised peptides, secreted from the gut in response to food, which augment secretion of insulin from pancreatic β-cells and inhibit inappropriate glucagon secretion. Glucagon-like peptide-1 has a circulating half-life of less than two minutes, due to rapid degradation by the enzyme dipeptidyl peptidase-4. Glucagon-like peptide-1 also slows gastric emptying, resulting in slower absorption of glucose following meals, enhances satiety and reduces appetite. Glucagon-like peptide-1 receptor agonists mimic endogenous GLP-1 activity but are resistant to breakdown by the DPP-4 enzyme, resulting in prolonged action.

Five GLP-1 receptor agonists are currently available, all in injectable formulations: albiglutide (once-weekly, to be discontinued in July 2018), dulaglutide (once weekly), exenatide (twice daily or once weekly), liraglutide (once daily) and lixisenatide (once daily).

9.1 GLYCAEMIC CONTROL

9.1.1 GLP-1 RECEPTOR AGONIST COMPARED WITH PLACEBO

Three placebo-controlled RCTs of 26 weeks duration were reported in a meta-analysis which demonstrated that in people with type 2 diabetes (disease duration 6–9 years, baseline BMI 30–34 kg/m^2) exenatide (10 micrograms twice daily) compared with placebo added to oral glucose-lowering agents (metformin and/or sulphonylurea) significantly reduced HbA1c (weighted mean difference (WMD) for change from baseline 0.95% (10.38 mmol/mol), 95% CI -1.21 to 0.7% (-13.22 to -7.65 mmol/mol)).[63] Those participants with a baseline HbA1c >9% (75 mmol/mol) had larger reductions in HbA1c. **1^{++}**

Four placebo-controlled RCTs of 26 weeks duration reported in a meta-analysis demonstrated that in people with type 2 diabetes (disease duration 5–9 years, baseline BMI 30.0–33.5 kg m^2) liraglutide (1.2–1.8 mg once daily) added to oral glucose-lowering agents (metformin and/or sulphonyurea or metformin and TZDs) significantly reduced HbA1c (WMD for change in HbA1c from baseline -1.0% (-10.93 mmol/mol), 95% CI -1.1 to -0.8% (12.02 to -8.74 mmol/mol)).[86] **1^{++}**

9.1.2 GLP-1 RECEPTOR AGONIST COMPARED WITH SULPHONYLUREA OR TZD

The NICE evidence review of first intensification of treatment found that the combination of a GLP-1 receptor agonist (exenatide, liraglutide or lixisenatide) with metformin resulted in a similar HbA1c reduction as a sulphonylurea and metformin combination at three months. The combination of exenatide and metformin was ranked first among comparators at this time point and had the highest probability of being more effective than the combination of metformin and sulphonylurea, but, after six months of treatment, the combination of metformin and liraglutide was more likely to be effective. By 12 months there were no significant differences in HbA1c reduction between the exenatide and metformin versus sulphonylurea and metformin combination.[4] A meta-analysis of two RCTs of 26 and 52 weeks duration, respectively, comparing liraglutide (1.2–1.8 mg once daily) with glimepiride (4–8 mg daily) reported no significant difference in HbA1c at the study endpoint.[86] **4** **1^{++}**

When comparing the addition of albiglutide, pioglitazone or placebo for patients already taking dual therapy with metformin and a sulphonylurea (glimepiride) over one year, albiglutide reduced HbA1c by 0.87% (9.51 mmol/mol) (95% CI 0.68% to 1.07% (7.43 to 11.69 mmol/mol)) compared with placebo; however, it did not meet prespecified non-inferiority margins for the comparison with pioglitazone (estimated difference 0.25% (2.73 mmol/mol), 95% CI 0.10% to 0.40% (1.09 to 4.37 mmol/mol)).[87] **1^{++}**

9.1.3 GLP-1 RECEPTOR AGONIST COMPARED WITH GLP-1 RECEPTOR AGONIST

In one RCT of 26 weeks duration, liraglutide 1.8 mg once daily added to oral glucose-lowering agents (metformin and sulphonylurea) reduced mean HbA1c by 1.12% (12.24 mmol/mol); in comparison exenatide 10 micrograms twice daily reduced HbA1c by 0.79% (8.63 mmol/mol). The estimated treatment difference was -0.33% (-3.61 mmol/mol), (95% CI 0.47 to -0.18% (-5.14 to -1.97 mmol/mol).[88] **1^{+}**

9.1.4 GLP-1 RECEPTOR AGONIST COMPARED WITH INSULIN

A meta-analysis reported data from two studies comparing exenatide therapy with insulin therapy. In both trials exenatide therapy added to oral glucose-lowering agents was compared with once-or twice-daily insulin added to oral glucose-lowering agents. Both exenatide and insulin therapy added to oral glucose-lowering agents resulted in a similar reduction in HbA1c, (WMD for change in HbA1c from baseline -0.06% (-0.66 mmol/mol), 95% CI -0.22 to 0.1% (-2.4 to 1.09 mmol/mol)).[63] **1++**

A further RCT of dulaglutide compared with insulin glargine U100 (both in combination with prandial insulin) showed the GLP-1 receptor agonist to be more effective in reducing HbA1c, albeit with a small effect size (mean difference 0.22% (-2.40 mmol/mol), 95% CI -0.38 to 0.07% (4.15 to 0.77 mmol/mol) and an open-label design.[89] Similarly, in those participants already on an optimal basal insulin the addition of once-weekly exenatide produced similar levels of HbA1c compared with the addition of prandial insulin lispro.[90] **1+**

In a further RCT, participants were randomised to receive albiglutide (30 mg once weekly) or insulin glargine U100 (10 U once daily) on a background of metformin and other therapy. At 52 weeks, HbA1c reduced by 0.66% (7.2 mmol/mol) with albiglutide and 0.81% (8.9 mmol/mol) with insulin glargine. On this basis, albiglutide met prespecified non-inferiority criteria (0.3% (3.3 mmol/mol)) for the comparison with insulin glargine.[91] **1+**

The NICE review concluded that a combination of metformin, a sulphonylurea and a GLP-1 receptor agonist had similar effects on HbA1c to a combination of metformin and NPH insulin.[4] **4**

9.1.5 COMBINATION THERAPY WITH GLP-1 RECEPTOR AGONIST AND INSULIN

One RCT randomised 413 individuals who were already on basal insulin and metformin to either insulin degludec or combination liraglutide/insulin degludec (once-daily, single subcutaneous injection). The liraglutide/insulin degludec combination produced a greater reduction in HbA1c than insulin alone (1.9% (21 mmol/mol) *v* 0.9% (10 mmol/mol)).[92,93] **1++** **1+**

Two RCTs have demonstrated that lixisenatide improves overall and postprandial hyperglycaemia when added to insulin glargine U100. In the first RCT, 495 patients with established basal insulin therapy but inadequate glycaemic control were randomised to lixisenatide 20 micrograms or placebo for 24 weeks. With lixisenatide, the placebo-corrected change of HbA1c from baseline was -0.4% (-4.37 mmol/mol) (95% CI -0.6 to 0.2% (6.56 to -2.19 mmol/mol)) and more participants attained target HbA1c <7% (28% *v* 12%, p<0.0001).[94] **1++**

In the second RCT, patients on dual oral glucose-lowering medication involving any combination of metformin, sulphonylureas, meglitinides or TZDs entered a 12-week run-in period, during which insulin glargine was added and systematically titrated. Eligible patients (fasting glucose ≤7.8 mmol/L and HbA1c 7–9%) were then randomised to lixisenatide 20 micrograms or placebo for 24 weeks while insulin titration continued. A greater reduction in HbA1c was observed with lixisenatide than with placebo (mean difference in change from baseline between groups -0.32% (-3.50 mmol/mol), 95% CI 0.46 to 0.17 (5.03 to -1.86 mmol/mol)) and a greater proportion of patients achieved target HbA1c <7% with lixisenatide than with placebo (56% *v* 39%, p<0.0001).[95] **1++**

Dulaglutide in combination with prandial insulin was more effective in reducing HbA1c than glargine U100 added to prandial insulin *(see section 9.1.4)*.

9.2 HYPOGLYCAEMIA, WEIGHT GAIN AND ADVERSE EFFECTS

Severe hypoglycaemia was rare in exenatide and liraglutide studies and occurred only when sulphonylureas were coprescribed.[86] Mild to moderate hypoglycaemia was seen in 16% of participants treated with exenatide compared with 7% receiving placebo (risk ratio 2.3, 95% CI 1.1 to 4.9).[63] In one study, 25.5% of patients treated with liraglutide versus 33.6% of patients treated with exenatide reported minor hypoglycaemia, p=0.01.[88] **1++** **1+**

NICE and AHRQ reviews of GLP-1 receptor agonists conclude that hypoglycaemia is less common with GLP-1 receptor agonists compared with sulphonylureas when used either as monotherapy or in combination with basal or premixed insulin.[3,4] **1++** **4**

Gastrointestinal (GI) adverse effects of GLP-1 receptor agonists are directly related to their mechanism of action (*see above*). The AHRQ review identified low-quality evidence that GLP-1 receptor agonists are associated with more GI adverse effects than metformin, sulphonylureas, TZDs or DPP-4 inhibitors. There is moderate-quality evidence of higher rates of GI adverse effects with GLP-1 receptor agonists in combination with metformin than with metformin alone and that the GLP-1 receptor agonist and metformin combination causes more GI adverse effects than metformin in combination with sulphonylureas.[3] **1++**

GLP-1 receptor agonist treatment is associated with weight loss, for example 1.6 to 3.1 kg with exenatide over 24 to 52 weeks.[96-100] People with type 2 diabetes treated with exenatide 10 micrograms twice daily versus liraglutide 1.8 mg once daily lost similar amounts of weight, 2.87 kg (SE, 0.33) versus -3.24 kg (SE 0.33), (estimated treatment difference -0.38 kg, 95% CI -0.99 to 0.23, p=0.22).[88] **1+**

In one RCT, albiglutide added to metformin was associated with greater weight loss than a sulphonylurea, but there was no difference for the comparison with sitagliptin. The rate of GI adverse effects was higher in the GLP-1 receptor agonist group compared with all other therapies.[101] In this trial, comparing albiglutide, pioglitazone and placebo in individuals on dual therapy with metformin and glimepiride, there was significant weight gain in the pioglitazone group over one year, but weight loss was similar with a GLP-1 receptor agonist and placebo.[87] **1+** **1++**

The fixed-ratio combination of liraglutide and insulin degludec (IDegLira) in patients on established oral glucose-lowering medication resulted in a significantly greater reduction in weight from baseline with the liraglutide/degludec combination (-2.7 kg) than with insulin degludec alone (0.0 kg), with similar rates of hypoglycaemia.[92] **1++**

Two trials in which lixisenatide was added to insulin glargine U100 for patients either established on basal insulin or newly titrated on basal insulin reported that reductions in body weight were greater with lixisenatide and the main adverse events with lixisenatide were gastrointestinal.[94,95] **1++**

Hence, weight loss is an advantage of GLP-1 receptor agonist therapy compared with insulin therapy and some oral glucose-lowering drugs, such as sulphonylureas and TZDs.

No dose adjustment is required for individuals with mild renal impairment and use of some agents should be avoided in people with severe renal impairment. However, the advice for use and dose alteration in people with moderate renal impairment varies between individual drugs within the GLP-1 receptor agonist class. Further information should be sought from the BNF and SPC.

9.3 CARDIOVASCULAR MORBIDITY AND MORTALITY

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) study randomised 9,340 individuals at high cardiovascular risk who were taking one or more oral antidiabetic medicines (excluding DPP-4 inhibitors) to 1.8 mg of liraglutide or matching placebo once daily in addition to standard of care.[102] There was a significant reduction in the primary outcome (composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke) with liraglutide compared with placebo over a median 3.8 years follow up (HR 0.87, 95% CI 0.78 to 0.97 for superiority). Cases of pancreatitis were numerically (but not statistically) lower with liraglutide, while cases of pancreatic neoplasm were numerically (but not statistically) higher. Additionally, the rate of developing nephropathy was reduced by 22% with liraglutide (p=0.003). **1++**

A further large cardiovascular outcome trial, Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA), demonstrated the cardiovascular safety (non-inferiority) of lixisenatide compared with placebo and standard of care over 25 months in 6,068 individuals with type 2 diabetes and recently diagnosed acute coronary syndrome. There was no increase in pancreatitis or pancreatic neoplasm.[103] **1++**

One of the largest cardiovascular outcome trials, EXenatide Study of Cardiovascular Event Lowering (EXSCEL), met its primary safety objective of non-inferiority of once-weekly exenatide versus placebo for major adverse cardiac events. However, the primary efficacy objective of a reduction in cardiovascular events did not reach statistical significance. In a prespecified secondary outcome analysis all-cause mortality was lower with exenatide than with placebo, but this was not statistically significant due to prespecification of a hierarchical testing plan.[104] 1++

R **GLP-1 receptor agonist therapy should be considered in people with a body mass index of ≥30 kg/m2** (or ethnicity-adjusted equivalent) **in combination with oral glucose-lowering drugs or basal insulin** (or both) **as third- or fourth-line treatment, when adequate glycaemic control has not been achieved with these drugs.**

R **GLP-1 receptor agonist therapy should be considered as an alternative to insulin in people for whom treatment with combinations of oral glucose-lowering drugs has been inadequate.**

R **For individuals with type 2 diabetes and established cardiovascular disease, GLP-1 receptor agonist therapies with proven cardiovascular benefit** (currently liraglutide) **should be considered.**

10 Insulin

When oral agents no longer provide effective glucose lowering, injectable therapy is required. In contrast to GLP-1 receptor agonists *(see section 9)*, insulin is associated with weight gain and hypoglycaemia.[105] However, it provides effective glucose lowering for individuals for whom GLP-1 therapy is not indicated (BMI <30 kg/m^2), not tolerated or contraindicated. Further information should be sought from the BNF and SPC. **1$^+$**

10.1 CONTINUING ORAL AGENTS WHEN INITIATING BASAL INSULIN

A systematic review showed that when starting once-daily insulin therapy, continuing metformin therapy is associated with lower HbA1c (by up to 0.6% (6.6 mmol/mol)) and less weight gain (by up to 3.7 kg) without an increase in the risk of hypoglycaemia.[106] Continuing sulphonylurea therapy in this context is associated with a greater HbA1c reduction (0.3% (3.3 mmol/mol), 95% CI 0.0 (0.0) to 0.6 (6.6)) than insulin monotherapy alone. However, post hoc analysis of the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial, which compared insulin glargine U100 with standard of care in 12,357 people with prediabetes or type 2 diabetes over 6.2 years, indicates that continuing sulphonylurea therapy independently predicts both severe and non-severe hypoglycaemia.[107] **1^{++}** **1$^+$**

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

✓ Consider stopping or reducing sulphonylurea therapy when insulin therapy is initiated. The benefits and risks of continuing other glucose-lowering agents should also be reviewed at this time on an individualised basis.

10.2 CHOOSING BASAL INSULIN

When starting insulin therapy as a single injection before bedtime, NPH insulin is as effective in reducing HbA1c as basal insulin analogue therapy.[108-112] However, basal insulin analogue therapy is associated with fewer episodes of nocturnal and overall hypoglycaemia, [112,113] although no difference was seen in severe hypoglycaemia. Collating evidence from six short-term trials, it was necessary to treat eight patients with type 2 diabetes (95% CI 6 to 11) with insulin glargine U100 compared with NPH (continuing oral agents) to avoid one episode of nocturnal hypoglycaemia.[114] Weight gain was slightly less with insulin detemir than with NPH insulin when added to oral glucose-lowering agents (1 kg, 95% CI -1.69 to -0.23 kg).[115] **1^{++}** **1$^+$**

More recently introduced longer-acting basal insulin analogues include insulin glargine U300 (300 units/ml, which is three times more concentrated than insulin glargine U100 (100 units/ml)) and insulin degludec. There are no trials directly investigating rates of hypoglycaemia with either of these agents compared with NPH insulin. However, there are three moderate-quality RCTs demonstrating lower rates of overall and nocturnal hypoglycaemia with insulin glargine U300 compared with insulin glargine U100,[116-118] and one moderate-quality 26-week extension study[119] of a 52-week RCT demonstrating lower rates of overall and nocturnal hypoglycaemia with insulin degludec compared with insulin glargine U100 (randomised 3:1).[120] **1$^+$**

In the DEVOTE trial, prespecified adjudicated severe hypoglycaemia occurred in 187 of 3,818 people with type 2 diabetes (4.9%) in the degludec group and in 252 of 3,819 people (6.6%) in the glargine U100 group, an absolute difference of 1.7% (rate ratio 0.60, p<0.001 for superiority; OR 0.73, p<0.001 for superiority).[121] **1^{++}**

R **Once-daily bedtime NPH insulin should be used when adding insulin to metformin. Basal insulin analogues should be considered according to hypoglycaemia risk, for example in those who suffer from recurrent episodes of hypoglycaemia or require assistance with insulin injections** (further information can be found in section 12.1).

✓ Careful clinical judgement must be applied to ensure insulin therapy is not delayed inappropriately.

10.3 INSULIN INITIATION AND INTENSIFICATION

In the largest (n=708) and longest (three-year) randomised trial of complex insulin regimens to date (4T), three insulin initiation regimens (basal, prandial, and biphasic) were compared. The regimen was intensified after one year if necessary to achieve a target HbA1c of 6.5% (48 mmol/mol) (if HbA1c was unacceptably high this occurred earlier).[122]

The basal insulin group commenced bedtime insulin detemir (or twice-daily dosing if required) with bolus mealtime insulin aspart added at intensification. The prandial group started with mealtime insulin aspart three times a day with subsequent intensification by addition of insulin detemir. The biphasic insulin group initially received twice daily biphasic insulin aspart, with later intensification by addition of insulin aspart at lunchtime. At three years, the basal initiation regimen (moving to additional prandial insulin) resulted in the best combination of outcomes. HbA1c reduction was equivalent with either basal or prandial insulin (6.9% (52 mmol/mol), 95% CI 6.6 to 7.1 (49 to 54 mmol/mol) *v* 6.8% (51 mmol/mol), 95% CI 6.6 to 7.0 (49 to 53 mmol/mol)); however, with the basal regimen there were fewer episodes per patient per year of grade 2 and 3 hypoglycaemia (median 1.7, 95% CI 1.3 to 2.0 *v* 5.7, 95% CI 4.3 to 7.0) with less weight gain (basal 3.6 kg *v* 6.4 kg, p<0.001). In comparison with biphasic insulin, the basal regimen resulted in lower HbA1c (7.1% (54 mmol/mol), 95% CI 6.9 to 7.3 (52 to 56 mmol/mol)), less weight gain (5.7 kg, p=0.005) and less hypoglycaemia (3 episodes (2.3 to 4.0) per patient per year) despite higher insulin doses (1.21 u/kg/day, 95% CI 1.08 to 1.34 *v* 0.86 u/kg/day, 95% CI 0.71 to 1.01). **1+**

The AHRQ review identified five further trials which confirmed no difference in HbA1c lowering when biphasic insulin compared with basal insulin was added to metformin therapy (0.3% (3.28 mmol/mol), 95% CI -0.3% to 0.9% (-3.28 to 9.84 mmol/mol) for three trials) but higher rates of hypoglycaemia.[3] **1++**

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

10.3.1 INTENSIFYING WITH PREMIXED PREPARATIONS

Adding in rapid-acting insulin in a premixed biphasic preparation results in lower HbA1c than with basal analogue therapy alone (HbA1c difference -0.39% (-4.26 mmol/mol), 95% CI -0.5 to -0.28% (-5.50 to -3.06 mmol/mol)).[123,124] However, the dose-titration algorithms used in nine of the 11 trials in one meta-analysis resulted in higher insulin doses being administered to participants receiving premixed biphasic insulin preparations compared with basal insulin analogue therapy.[124] Consequently, there was a greater risk of hypoglycaemia (OR 2.02, 95% CI 1.35 to 3.04) and significantly greater weight gain (mean 0.6 to 1.9 kg in three studies with premixed insulin analogues compared with basal insulin analogues).[125] **1++** **1+**

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

10.3.2 INTENSIFYING WITH RAPID-ACTING INSULIN ANALOGUES VERSUS HUMAN INSULIN

No difference in HbA1c reduction has been demonstrated between premixed preparations containing rapid-acting analogues compared with those containing regular insulin (HbA1c difference -0.05% (-0.55 mmol/mol), 95% CI -0.15 to 0.04% (-1.64 to 0.44 mmol/mol)), although there was a borderline increase in rates of hypoglycaemia (OR 1.5, 95% CI 1.0 to 2.26) with analogue mixtures.[124] In four times daily (basal-bolus) regimens, regular insulin is as effective as rapid-acting analogue insulin for HbA1c reduction in type 2 diabetes, with no difference in rates of hypoglycaemia.[108,126,127] **1+**

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

11 Algorithm for glucose lowering

1st LINE
In ADDITION to lifestyle measures

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

	USUAL APPROACH	ALTERNATIVE APPROACH: if osmotic symptoms or intolerant of metformin
	METFORMIN*	SULPHONYLUREA*
EFFICACY	MODERATE	HIGH
CV BENEFIT	YES	NO
HYPOGLYCAEMIA RISK	LOW	HIGH
WEIGHT	REDUCTION	GAIN
MAIN ADVERSE EVENTS	GASTROINTESTINAL	HYPOGLYCAEMIA
IN CKD STAGE 3A	MAXIMUM 2 g DAILY	CAREFUL MONITORING [1]

ONCE OSMOTIC SYMPTOMS RESOLVED, ADD

The following are also accepted by the SMC for first-line use where metformin and sulphonylureas are not tolerated:

- *canagliflozin, dapagliflozin or empagliflozin (SGLT2 inhibitors);*
- *linagliptin, sitagliptin or vildagliptin (DPP-4 inhibitors);*
- *pioglitazone (thiazolidinedione)*

IF SEVERE OSMOTIC SYMPTOMS WITH WEIGHT LOSS OR POSSIBILITY OF TYPE 1 DIABETES **(URGENT - PHONE SECONDARY CARE IMMEDIATELY)**

2nd LINE
In ADDITION to lifestyle measures

IF NOT REACHING TARGET AFTER 3–6 MONTHS [2], REVIEW ADHERENCE: THEN GUIDED BY PATIENT PROFILE

ADD ONE OF:

	SULPHONYLUREA* *OR*	SGLT2 INHIBITOR* *OR*	DPP-4 INHIBITOR* *OR*	PIOGLITAZONE*
EFFICACY	HIGH	MODERATE	LOW/MODERATE	MODERATE
CV BENEFIT	NO	YES (SPECIFIC AGENTS) [3]	NO	PROBABLE (BUT FLUID RETENTION)
HYPOGLYCAEMIA RISK	HIGH	LOW	LOW	LOW
WEIGHT	GAIN	LOSS	NEUTRAL	GAIN
MAIN ADVERSE EVENTS	HYPOGLYCAEMIA	GENITAL MYCOTIC	FEW	OEDEMA/FRACTURES [6]
IN CKD STAGE 3A	CAREFUL MONITORING [1]	DO NOT INITIATE [4]	REDUCE DOSE [5]	DOSE UNCHANGED

3rd LINE
In ADDITION to lifestyle measures

IF NOT REACHING TARGET AFTER 3–6 MONTHS, REVIEW ADHERENCE: THEN GUIDED BY PATIENT PROFILE [7]

ADD *EITHER* AN ADDITIONAL ORAL AGENT FROM A DIFFERENT CLASS

	SULPHONYLUREA* *OR*	SGLT2 INHIBITOR* *OR*	DPP-4 INHIBITOR* *OR*	PIOGLITAZONE*
	If BMI >30 kg/m²		**OR AN INJECTABLE AGENT**	*If BMI <30 kg/m²*
	GLP-1 AGONIST*		BASAL INSULIN*	
EFFICACY	HIGH	• stop DPP-4 inhibitor • consider reducing sulphonylurea • continue metformin • can continue pioglitazone • can continue SGLT2 inhibitor	HIGH	• inject before bed • use NPH (isophane) insulin - or longer-acting analogues according to risk of hypoglycaemia [10] • can continue metformin, pioglitazone, DPP-4 inhibitor or SGLT2 inhibitor • can reduce or stop sulphonylurea
CV BENEFIT	YES (SPECIFIC AGENTS) [3]		NO	
HYPOGLYCAEMIA RISK	LOW		HIGHEST	
WEIGHT	LOSS		GAIN	
MAIN ADVERSE EVENTS	GASTROINTESTINAL		HYPOGLYCAEMIA	
IN CKD STAGE 3A	DOSE UNCHANGED [8]		DOSE UNCHANGED [9]	

IF INSULIN INTENSIFICATION REQUIRED (NEED SPECIALIST INPUT)

4th LINE
In ADDITION to lifestyle measures

IF NOT REACHING TARGET AFTER 3–6 MONTHS, REVIEW ADHERENCE: THEN GUIDED BY PATIENT PROFILE ADD ADDITIONAL AGENT(S) FROM 3rd LINE OPTIONS *(NEED SPECIALIST INPUT)*

ADD PRANDIAL INSULIN OR SWITCH TO TWICE-DAILY MIXED BIPHASIC INSULIN

Algorithm summarises evidence from the guideline in the context of the clinical experience of the Guideline Development Group. It does not apply in severe renal or hepatic insufficiency.

Prescribers should refer to the British National Formulary (www.medicinescomplete.com), the Scottish Medicines Consortium (www.scottishmedicines.org.uk) and Medicines and Healthcare products Regulatory Agency (MHRA) warnings for updated guidance on licensed indications, full contraindications and monitoring requirements.

***Continue medication at each stage if EITHER individualised target achieved OR HbA1c falls more than 0.5% (5.5 mmol/mol) in 3–6 months. Discontinue if evidence that ineffective.**

NOTES: 1. Consider dose reduction, **2**. Do not delay if first line options not tolerated / inappropriate, **3.** See guideline pages 23 & 26-27, **4.** See BNF: specific agents can be continued at reduced dose, **5.** See BNF: no dose reduction required for linagliptin **6**. Pioglitazone is contraindicated in people with (or with a history of) heart failure or bladder cancer, **7.** Do not combine dapagliflozin with pioglitazone, **8.** Caution with exenatide when eGFR<50 ml/min/1.73 m², **9.** Adjust according to response, **10**. Driving, occupational hazards, risk of falls, previous history.

ABBREVIATIONS: CKD 3A = chronic kidney disease stage 3A (estimated glomerular filtration rate 45–59 ml/min/1.73 m²) CV = cardiovascular

12 Provision of information

This section reflects the issues likely to be of most concern to people with type 2 diabetes and their carers. These points are provided for use by health professionals when discussing glucose lowering with people with type 2 diabetes and their carers and in guiding the development of locally-produced information materials.

12.1 CHECKLIST FOR PROVISION OF INFORMATION

This section gives examples of the information people with type 2 diabetes or their carers may find helpful throughout the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive. The information contained in this section should be discussed in formats which are most helpful for their comprehension and engagement.

People with diabetes may have to take a range of oral and injectable medications each of which is associated with different properties and warnings. Information is presented below on each of the major classes of glucose-lowering agents. A number of oral agents are available in combination with each other in fixed-dose combination. Using these preparations to decrease 'tablet burden' is associated with increased concordance with therapy. This can also be achieved by stopping therapies for which risks are likely to be greater than benefits.

12.1.1 PRINCIPLES

Established relationships between people with diabetes and their healthcare professionals, together with agreed individualised targets for care, are critical for realising the potential benefits of clinic consultations and resulting prescriptions. Wherever possible, members of the diabetes care team should adopt an open attitude. Prescribing should be tailored to needs and circumstances, taking into account personal preferences, comorbidities, and risks from polypharmacy. Such an approach is especially important in the context of multimorbidity. In order that appropriate guidelines may be followed, people should be advised to inform healthcare professionals who are treating comorbid conditions of their diabetes.

12.1.2 METFORMIN

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

A modified-release preparation (metformin MR) is also available. Some individuals otherwise intolerant of metformin may find this more acceptable, It should be started once-daily but may be intensified to split daily doses.

Metformin should be discontinued during a severe illness (eg myocardial infarction, pneumonia, severe infection and/or dehydration) as it may aggravate tissue hypoxia and accumulate when renal function is impaired (eGFR <45 ml/min/1.73 m^2). In these circumstances, it may be appropriate to use other glucose-lowering therapies, including insulin, in which case admission to hospital may be required.

As iodine-containing contrast media may cause acute deterioration of renal function, local arrangements should be in place for discontinuation of metformin prior to either i) intra-arterial radiological or cardiology investigations/interventions when eGFR is lower than 45 ml/min/1.73 m^2, or ii) intravenous or intra-arterial procedures when eGFR is deteriorating due to illness *(see www.ranzcr.com/search/ranzcr-iodinated-contrast-guidelines)*.

Fasting presents little hazard in people who take only metformin to manage glucose levels. For those fasting during Ramadan, for example, if a dose is usually taken at lunchtime it can be omitted or taken with the sunset meal instead.

12.1.3 SULPHONYLUREAS

These agents, most commonly gliclazide and glimepiride, should ideally be taken 30 minutes before food. They are particularly useful for rapid control of blood glucose and relief of symptoms including thirst, polyuria and weight loss. They are more effective early in the management of type 2 diabetes. Their main side effects are hypoglycaemia and weight gain.

The warning signs of hypoglycaemia, which should be outlined to people taking these agents, include (early signs) tremor, sweating, shaking, irritability, and (later signs) lack of concentration and co-ordination. People prescribed sulphonylureas should be prescribed adequate supplies of blood glucose test strips as per the local formulary. The risk of hypoglycaemia is higher in older age groups, and in those with renal impairment and/or liver disease; this risk may be underestimated by RCTs.

The Driver and Vehicle Licensing Agency (DVLA) requires holders of group 2 licenses (bus and lorry drivers) to notify them when using any glucose-lowering medication. Those taking sulphonylureas must be able to provide evidence of checking blood glucose at least twice per day and at times relevant to driving. Holders of group 1 licenses (car drivers and motorcyclists) need not notify the DVLA provided they have experienced no more than one episode of severe hypoglycaemia in the last 12 months and, if needed, check blood glucose at times relevant to driving and are under regular review. Detailed guidance can be found at www.gov.uk/guidance/diabetes-mellitus-assessing-fitness-to-drive#diabetes-treated-by-medication-other-than-insulin.

Gliclazide is available in an MR preparation. This permits once-daily dosing even when higher doses are required. Prescribers should be aware that gliclazide MR 30 mg is therapeutically equivalent to standard gliclazide 80 mg (maximum dose therefore 120 mg once daily rather than 160 mg twice daily). Individuals using gliclazide should not be prescribed the antifungal miconazole due to an increase in the hypoglycaemic effect.

Individuals taking a short-acting sulphonylurea, (eg gliclazide) who are fasting, for example during Ramadan, may be advised to take the largest dose with their evening meal and, if necessary, to halve their morning dose. Longer-acting sulphonylureas, such as glimepiride, are more hazardous and should be avoided while fasting.

People taking sulphonylureas in the longer term should also be advised of their propensity to cause weight gain.

12.1.4 THIAZOLIDINEDIONES

People prescribed pioglitazone should be advised that they might experience ankle oedema. Where this occurs, discontinuation is usually appropriate. If taking this agent in the longer term, they should be advised of the likelihood of weight gain and increased risk of fracture and heart failure. People prescribed pioglitazone should be counselled to seek medical advice if they experience haematuria, dysuria or pelvic pain in view of the association with bladder cancer. No changes to pioglitazone regimens are required during fasting including Ramadan.

12.1.5 DPP-4 INHIBITORS

These agents (alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin) are generally well tolerated and rarely cause hypoglycaemia. They may be useful if ongoing glucose-lowering therapy is required during periods of fasting, for example Ramadan.

Dose reductions are required for individuals with renal impairment (eGFR < 60 ml/min/1.73 m^2) taking DPP-4 inhibitors other than linagliptin.

12.1.6 SGLT2 INHIBITORS

Although DKA is uncommon with SGLT2 inhibitors, those who are prescribed them should be made aware of the risk and how to recognise the symptoms, including rapid weight loss, nausea or vomiting, stomach pain, excessive thirst, fast and deep breathing, confusion, unusual sleepiness or tiredness, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat. In this situation, the SGLT2 inhibitor should be stopped and urgent medical attention sought. Further information on prevention and immediate management of this risk is available from the Association of British Clinical Diabetologists position statement (*see www.diabetologists-abcd.org.uk/Position_Papers/ABCD_DKA_SGLT2.pdf*).

There is a small risk of developing a genital yeast or fungal infection (most commonly thrush in women) when taking SGLT2 inhibitors due to more glucose being excreted in the urine. These infections are easily treated with over-the-counter treatments. The prescribing doctor should be informed as treatment may need to be changed if infections recur. People taking these medications should be advised of the need for scrupulous personal hygiene to try to reduce the risk of these infections.

For those who are fasting, for example, during Ramadan, no change in SGLT2 inhibitor dose is required, although individuals should be reminded to stay adequately hydrated (at least two litres of water per day). If blood glucose is very high (>20 mmol/L) and rising, or if dehydrated and experiencing symptoms of DKA (*see above*), urgent medical attention should be sought.

12.1.7 GLP-1 RECEPTOR AGONISTS

These agents are injected subcutaneously. On initiation, people with diabetes should be informed that their injections are not insulin as this can lead to confusion in interactions with other health professionals. In keeping with the appetite-suppressant effect of these agents (albiglutide, dulaglutide, exenatide, liraglutide and lixisenatide) the most common adverse effects are nausea, vomiting and diarrhoea. Increased contact with the diabetes team is required particularly in the first weeks of use, usually with monitoring of the therapeutic response - weight and HbA1c. These adverse GI symptoms associated with GLP-1 receptor agonists can be minimised with careful dose titration and often abate within weeks.

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

GLP-1 receptor agonists may be continued as usual for individuals who are fasting during Ramadan with a single injection before the sunset meal. If there is significant nausea the dose can be reduced by 50%.[128]

People taking GLP-1 receptor agonists may hold a regular (Group 1) driving licence without restriction, but must notify the DVLA if they hold a Group 2 licence.

12.1.8 INSULIN

When starting insulin therapy in adults with type 2 diabetes, a structured education programme should be used to guide insulin dose titration, including:

- injection technique (rotating injection sites)
- self monitoring of blood glucose
- dose titration to target glucose levels
- dietary understanding
- management of acute changes in plasma glucose control
- management of hypoglycaemia
- DVLA driving requirements (including adequate awareness of hypoglycaemia, no more than one episode of severe hypoglycaemia in the preceding 12 months, evidence of recommended rates of blood glucose monitoring) (*see www.gov.uk/government/uploads/system/uploads/attachment_data/file/596959/assessing-fitness-to-drive-a-guide-for-medical-professionals*)
- continuing support (including by telephone) from appropriately trained and experienced health professionals.

Individuals for whom basal analogues may be more appropriate than NPH basal insulin include:

- those who suffer from recurrent episodes of hypoglycaemia, particularly at night
- those for whom hypoglycaemia could cause increased risk to themselves or others, for example occupational driving, working with heavy machinery, working at heights (if this cannot be avoided), or caring for young or otherwise vulnerable individuals
- those who need assistance from a carer or healthcare professional to inject insulin and use of a long-acting basal insulin analogue would reduce the frequency of injections from twice to once daily
- those whose lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes
- those who would otherwise need twice-daily NPH insulin injections.

When commencing insulin glargine U300, the summary of product characteristics recommends reducing the dose by 20% either when switching from twice-daily basal insulin to once-daily insulin glargine U300, or if switching back from once-daily insulin glargine U300 to once-daily insulin glargine U100.

Rapid-acting analogues (whether as bolus insulin or as a component of premixed insulin) may be appropriate for:

- those who prefer to inject insulin immediately before a meal
- those having problems with hypoglycaemia
- those in whom blood glucose rises markedly after meals.

People with diabetes should have a clear plan of how to get help on an urgent or semi-urgent basis. This will often involve the local diabetes team in office hours, but outwith these times arrangements vary across Scotland. If admitted to hospital they should be aware that the Diabetes Team can be asked to advise on the management of their diabetes while they are in hospital, particularly if they have a concern.

In those who are fasting, for example during Ramadan, due to the increased risks of hypoglycaemia, insulin regimens should be individualised according to the diet, baseline glycaemic control, level of physical activity, and blood glucose monitoring of the person. In general, sharp reductions in the total daily dose of insulin are not required. For those taking twice-daily premixed insulin injections, the morning and evening doses may be reversed if the morning dose is usually larger. If the doses are the same, the morning dose may be halved and a corresponding larger dose taken before the sunset meal. Alternatively, a basal-bolus regimen may be offered, with the basal insulin taken with the larger sunset meal.

12.2 SOURCES OF FURTHER INFORMATION

Diabetes in Scotland

www.diabetesinscotland.org.uk

The Scottish Diabetes Group is a national Steering Group which co-ordinates and evaluates the implementation of the Scottish Diabetes Framework and Action Plan. It also oversees the development of the national diabetes strategy and provides expert advice to the Scottish Government Health Directorates. Its website provides advice leaflets, reports and survey results, in addition to information regarding research and education.

Diabetes UK (Scottish office)

The Venlaw, 349 Bath Street, Glasgow, G2 4AA
Tel: 0141 245 6380 • Careline: 0845 120 2960
www.diabetes.org.uk • Email: scotland@diabetes.org.uk

Diabetes UK provides a range of information on diabetes including leaflets, fact sheets and Diabetes UK's magazine Balance. They provide advice on all aspects of diabetes including diabetic care, diet, holidays and insurance.

Driver and Vehicle Licensing Agency

www.gov.uk/diabetes-driving

The Driver and Vehicle Licensing Agency is an executive agency of the Department for Transport and its responsibilities include issuing driving licenses, recording driver endorsements and medical conditions and issuing vehicle registration certificates.

Healthtalk

www.healthtalk.org

Healthtalk online is the website of the Database of Individual Patients' Experience of illness (DIPEx) charity. It provides access to people's experiences of living with diabetes.

My Diabetes My Way

www.mydiabetesmyway.scot.nhs.uk

This is an NHSScotland interactive diabetes website to help support people who have diabetes and their family and friends. It provides leaflets, videos, educational tools and games containing information about diabetes.

13 Implementing the guideline

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

13.1 IMPLEMENTATION STRATEGY

Implementation of national clinical guidelines is the responsibility of each NHS board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

Implementation of this guideline will be encouraged and supported by SIGN. The implementation strategy for this guideline encompasses the following tools and activities.

13.2 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

No recommendations are considered likely to reach the £5 million threshold which warrants full resource impact analysis.

13.3 AUDITING CURRENT PRACTICE

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

The guideline development group has identified the following as key points to audit to assist with the implementation of this guideline:

- the proportion of individuals with type 2 diabetes for whom metformin or sulphonylureas are tolerated and not contraindicated that is prescribed either drug as first-line therapy
- the proportion of individuals with type 2 diabetes for whom metformin is not tolerated or is contraindicated that is prescribed a sulphonylurea as first-line therapy
- the proportion of individuals on long-term pioglitazone that has received fracture risk assessment
- the proportion of individuals with type 2 diabetes and established cardiovascular disease receiving a GLP-1 receptor agonist that is prescribed liraglutide.

13.4 HEALTH TECHNOLOGY ASSESSMENT ADVICE FOR NHSSCOTLAND

The Scottish Medicines Consortium has published advice on a range of drugs used for glucose lowering in people with type 2 diabetes: (www.scottishmedicines.org.uk/SMC_Advice/Advice_Directory/DrugsBySubCategory?term=6.1%20Drugs%20used%20in%20diabetes).

In May 2016, NICE published a technology appraisal on canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes.[71] This superseded SMC advice (for the indication of monotherapy only) and was endorsed by Healthcare Improvement Scotland.

14 The evidence base

14.1 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology with adaptations to facilitate a rapid review. Secondary evidence was derived from two sources.

Firstly, a comprehensive series of systematic reviews and meta-analyses, published by the AHRQ, of studies that assessed intermediate and clinical outcomes or safety for monotherapy or metformin-based combination therapy comparisons.[3] This identified 216 relevant studies published between 2009 and 2015 which were combined, where possible, in meta-analyses. Secondly, the evidence-based guideline developed by NICE on type 2 diabetes in adults.[4] This was an update to the previous NICE guideline and the 2015 version included a systematic review of drug treatment to control blood glucose from literature published between 2007 and 2014. NICE also completed a series of network meta-analyses (NMAs) to simultaneously compare multiple treatments in a single meta-analysis while preserving the randomisation of the included trials in the reviews.

These sources of secondary evidence were supplemented by a systematic review of primary literature carried out using an explicit search strategy devised by a SIGN Evidence and Information Scientist. Databases searched included Cochrane Central Register of Controlled Trials (CENTRAL), National Institute for Health Research-Health Technology Assessment (NIHR-HTA), Medline, Medline In-Process, Embase and the Cochrane Library. The year range covered was 2014–2016 (2011–2016 for SGLT2 inhibitors). Internet searches were carried out on various websites including the US National Guidelines Clearinghouse.

The main searches were supplemented by material identified by individual members of the development group. In addition, RCTs of antidiabetic drugs with cardiovascular outcomes which were published during the development period of the guideline were added, up to a deadline of September 2017.

The following exclusion criteria were applied to the SIGN literature reviews:

- RCTs with less than 24 weeks duration
- RCTs with a patient population not representative (in general) of Scotland
- RCTs with a small sample size (experimental/control groups n<200)
- RCTs involving products without a marketing authorisation in Scotland.

Due to the rapid review methodology adopted, cost effectiveness was not included as an outcome for the key questions (*see Annex 1*). Each of the selected papers was evaluated by two Evidence and Information Scientists using standard SIGN methodological checklists before conclusions were considered as evidence by the guideline development group.

14.2 RECOMMENDATIONS FOR RESEARCH

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline *(see Annex 1)*. The following areas for further research have been identified:

- Of the currently-available glucose-lowering therapies, which should be used first line for optimal long-term microvascular and cardiovascular outcomes?
- What is the best sequential combination of glucose-lowering therapies for optimal long-term microvascular and cardiovascular outcomes?
- When HbA1c is not to target on basal insulin, is adding GLP-1 receptor agonist therapy or prandial insulin more effective for HbA1c, weight, hypoglycaemia, and long-term microvascular and cardiovascular outcomes?
- What causes adverse outcomes in people with type 2 diabetes with long duration of disease when using an HbA1c target of 6.0%, and how can such harm be avoided?
- What is the most appropriate glucose target for people with type 2 diabetes and multimorbidities? What is the optimal therapeutic combination to achieve this?
- Can novel genetic, proteomic, metabolomic or other biomarkers guide prescribing of oral glucose-lowering agents in people with type 2 diabetes, ie predict individual patient HbA1c responses?

15 Development of the guideline

15.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of Healthcare Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising healthcare professionals using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in 'SIGN 50: A Guideline Developer's Handbook', available at **www.sign.ac.uk**

This guideline was developed according to the 2015 edition of SIGN 50 with adaptations.

15.2 THE GUIDELINE DEVELOPMENT GROUP

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The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest. A register of interests is available in the supporting material section for this guideline at **www.sign.ac.uk**

Guideline development and literature review expertise, support and facilitation were provided by SIGN Executive and Healthcare Improvement Scotland staff. All members of the SIGN Executive make yearly declarations of interest A register of interests is available on the contacts page of the SIGN website **www.sign.ac.uk**

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15.2.1 ACKNOWLEDGEMENTS

SIGN would like to acknowledge the guideline development group responsible for the development of section 6 of SIGN 116: Management of diabetes, on which this guideline is based.

SIGN is also grateful to the following former member of the guideline development group who contributed to the development of the guideline.

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15.3 CONSULTATION AND PEER REVIEW

15.3.1 SPECIALIST REVIEW

This guideline was reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments. A report of the peer review comments and responses is available in the supporting material section for this guideline on the SIGN website. All expert referees made declarations of interest and further details of these are available on request from the SIGN Executive.

SIGN is very grateful to all of these experts for their contribution to the guideline.

Professor Steve Bain	*Professor in Medicine (Diabetes), Swansea University Medical School*
Professor Anthony Barnett	*Professor of Medicine, University of Birmingham and Honorary Consultant Physician and Clinical Director, Diabetes/Endocrinology/Weight Management, Heart of England NHS Foundation Trust, Birmingham*
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Dr Marc Evans	*Consultant Diabetologist, Llandough Hospital, Cardiff and the University Hospital of Wales College of Medicine*
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Association of the British Pharmaceutical Industry Scotland

NHSScotland Special Interest Group Diabetes: Pharmacy

Royal College of Pathologists

Royal College of Physicians of Edinburgh

15.3.2 PUBLIC CONSULTATION

The draft guideline was also available on the SIGN website for three weeks to allow all interested parties to comment. The draft algorithm for glucose lowering was available separately as public consultation for two weeks.

15.3.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows. All members of SIGN Council make yearly declarations of interest. A register of interests is available on the SIGN Council membership page of the SIGN website **www.sign.ac.uk**

Dr Roberta James	*SIGN Programme Lead; Co-Editor*
Professor John Kinsella	*Chair of SIGN; Co-Editor*
Dr Jenny Bennison	*Vice-chair of SIGN*
Mr Gary Cook	*Royal Pharmaceutical Society*
Dr Susan Myles	*Unit Head, Scottish Health Technologies Group and Lead Health Economist, Healthcare Improvement Scotland*

Abbreviations

4T	Treating to Target in Type 2 Diabetes trial
ACCORD	Action to Control Cardiovascular Risk in Diabetes trial
ACE	Acarbose Cardiovascular Evaluation trial
ADOPT	A Diabetes Outcome Progression trial
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trial
AHRQ	Agency for Healthcare Research and Quality
ARI	absolute risk increase
ARR	absolute risk reduction
BMI	body mass index
BNF	British National Formulary
CANVAS	CANagliflozin cardioVascular Assessment Study
CARMELINA	Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus
CAROLINA	CARdiovascular Outcome trial of LINAgliptin Versus Glimepiride in Type 2 Diabetes
CENTRAL	Cochrane Central Register of Controlled Trials
CHF	chronic heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CREDENCE	Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation trial
CV	cardiovascular
CVD	cardiovascular disease
DECLARE-TIMI	Dapagliflozin Effect on CardiovascuLAR Events - Thrombolysis in Myocardial Infarction trial
DEVOTE	Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events
DIPEx	Database of Individual Patients' Experience of illness
DKA	diabetic ketoacidosis
DPP-4	dipeptidyl peptidase-4
DVLA	Driver and Vehicle Licensing Agency
eGFR	estimated glomerular filtration rate
ELIXA	Evaluation of Lixisenatide in Acute Coronary Syndrome trial
EMA	European Medicines Agency
EMPA-REG	The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose

EU	European Union
EXAMINE	EXamination of cArdiovascular outcoMes with alogliptIN versus standard of care trial
EXSCEL	EXenatide Study of Cardiovascular Event Lowering trial
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GMC	General Medical Council
HbA1c	glycated haemoglobin
HDL	high-density lipoprotein
HR	hazard ratio
LDL	low-density lipoprotein
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results trial
MA	marketing authorisation
MI	myocardial infarction
MR	modified release
MTA	Multiple Technology Appraisal
NICE	National Institute for Health and Care Excellence
NIHR-HTA	National Institute for Health Research - Health Technology Assessment
NMA	network meta-analysis
NNT	number needed to treat
NPH	neutral protamine Hagedorn
NYHA	New York Heart Association
OR	odds ratio
ORIGIN	Outcome Reduction with an Initial Glargine Intervention trial
RCT	randomised controlled trial
RR	relative risk or rate ratio
SAVOR-TIMI	Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus-Thrombolysis in Myocardial Infarction trial
SE	standard error
SGLT2	sodium glucose co-transporter 2
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SMD	standardised mean difference
SPC	summary of product characteristics
TECOS	Trial to Evaluate Cardiovascular Outcomes after treatment with Sitagliptin

TZD	thiazolidinedione
UKPDS	United Kingdom Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial
WMD	weighted mean difference

Annex 1

Key questions addressed in this update

This guideline is based on a series of structured key questions that define the target population, the intervention, diagnostic test, or exposure under investigation, the comparison(s) used and the outcomes used to measure efficacy, effectiveness, or risk. These questions form the basis of the systematic literature search.

Guideline section	Key question	
3	1	In adult patients with type 2 diabetes, what is the evidence that reducing HbA1c to specified targets (<7.5%) affects mortality, cardiovascular morbidity and mortality, microvascular morbidity, weight, hypoglycaemia and other adverse events? *(Carried over without update from SIGN 116)*
4, 5	2	In adults with type 2 diabetes what is the evidence that metformin or sulphonylureas affect mortality, cardiovascular morbidity and mortality, microvascular morbidity, HbA1c, weight, hypoglycaemia and other adverse events?
6	3	In adults with type 2 diabetes what is the evidence that alpha-glucosidase inhibitors or thiazolidinediones affects mortality, cardiovascular morbidity and mortality, microvascular morbidity, HbA1c, weight, hypoglycaemia and other adverse events?
7, 9	4	In adults with type 2 diabetes what is the evidence that DPP-4 inhibitors or GLP-1 receptor agonists affect mortality, cardiovascular morbidity and mortality, microvascular morbidity, HbA1c, weight, hypoglycaemia and other adverse events?
8	5	In adults with type 2 diabetes what is the evidence that SGLT2 inhibitors affect mortality, cardiovascular morbidity and mortality, microvascular morbidity, HbA1c, weight, hypoglycaemia and other adverse events?
10	6	In adults with type 2 diabetes what is the evidence that insulin affects mortality, cardiovascular morbidity and mortality, microvascular morbidity, HbA1c, weight, hypoglycaemia and other adverse events?

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ISBN 978 1 909103 61 0

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