Healthcare Improvement Scotland

SIGN
Scottish Intercollegiate Guidelines Network

Pharmacological management of glycaemic control in people with type 2 diabetes

A national clinical guideline

PEER REVIEW DRAFT May 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 of RCTs, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2^{++}	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding 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 '**conditiona**l' 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.

Contents

1 Introduction

1.1 THE NEED FOR A GUIDELINE

The immediate purpose of lowering blood glucose is to provide relief from symptoms (thirst, polyuria, nocturia, and blurred vision). Thereafter, the aim is to prevent microvascular complications: loss of vision (retinopathy), renal failure (nephropathy), and foot ulceration (neuropathy). High blood glucose (hyperglycaemia) is also one of the features of diabetes, with raised blood pressure and cholesterol, 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 referenced 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

The structure and some of the content in this guideline was originally published in SIGN 116, Management of diabetes. 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 the new Scottish Diabetes Prescribing Strategy a decision was made to release this updated version as a stand-alone 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 four 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,[2] the NICE clinical guideline on type 2 diabetes in adults, published in 2015[3] and new searches for primary literature carried out to update these sources to 2017. See section 15.1 for further information about the SIGN systematic review.

1.2 REMIT OF THE GUIDELINE

1.2.1 OVERALL OBJECTIVES

This guideline focuses on: (i) optimal targets for glucose control for the prevention of microvascular and macrovascular complications (unchanged from SIGN 116); and, (ii) the risks and benefits of the principal therapeutic classes of glucose-lowering agents (oral/injectable) and insulins currently available for those who require measures beyond diet and exercise to achieve targets, (updated from SIGN 116). An updated algorithm to guide choice of first-, second- and third-line glucose-lowering agent which incorporates the summarised evidence and the clinical experience of the guideline development group is in development (*not available in this version*).

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/ adverse effects	Updated
4.3	Metformin – cardiovascular morbidity and mortality	Minor update
5.1	Sulphonylureas – glycaemic control	Updated
5.2	Sulphonylureas – hypoglycaemia/weight gain/ 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/ adverse effects	Updated
7.3	Dipeptidyl peptidase-4 inhibitors – cardiovascular morbidity and mortality	Completely revised
8.2	Alpha-glucosidase inhibitors – hypoglycaemia/weight gain/ adverse effects	Updated
9.1	Glucagon like Peptide-1 agonists – glycaemic control	Updated
9.2	Glucagon like Peptide-1 agonists – hypoglycaemia/weight gain/ adverse effects	Updated
9.3	Glucagon like Peptide-1 agonists – cardiovascular morbidity and mortality	Completely revised
10	Sodium Glucose Co-Transporter 2 inhibitors	New
11.1	Continuing oral agents when initiating basal insulin	Updated
11.2	Initiating basal insulin: long-acting insulin analogues versus intermediate-acting human insulin	Updated
11.3	Insulin initiation and intensification: basal versus prandial versus premixed insulins	Minor update
11.4	Intensifying insulin therapy	Minor update
12	Algorithm for glucose lowering in people with type 2 diabetes	Completely revised
13.1	Checklist for provision of information	*Not available in this version*

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, general practitioners, pharmacists, as well as patients, 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 (MA) 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 MA 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.[4]

"Prescribing medicines outside the conditions of their marketing authorisation alters (and

probably increases) the prescribers' professional responsibility and potential liability".[4]

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).[5] The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers.[6]

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 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.

In addition, Healthcare Improvement Scotland reviews Multiple Technology Appraisals (MTAs) produced by the National Institute for Health and Care Excellence (NICE) and provides advice about their applicability in NHSScotland. If Healthcare Improvement Scotland advises that MTA guidance is 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 the section on implementation.

2 Key recommendations

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

NOT AVAILABLE IN THIS DRAFT

3 Targets for glycaemic control

3.1 EVIDENCE FOR 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.[7] 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.[8] 1+

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study used modified-release gliclazide (MR) then increased metformin, thiazolidinedione, acarbose and insulin (initial basal with prandial added as required) to reduce HbA1c to a mean of 6.5% (48 mmol/mol) compared with a mean of 7.3% (56 mmol/mol) from a baseline of 7.5% (58 mmol/mol) by aiming for a target of <6.5% (48 mmol/mol) as compared with standard care. Mean duration of diabetes in this trial was 7.9 years.[9] 1+

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study used the standard range of presently available therapy (including sulphonylureas, metformin, thiazolidinediones, insulin, DPP-4 inhibitors and exenatide) to reduce HbA1c rapidly to a mean of 6.4% (46 mmol/mol) compared with a mean of 7.5% (58 mmol/mol) from a baseline of 8.3% (67 mmol/mol) by aiming for a target of 6.0% (42 mmol/mol) as compared with a target of 7.0 to 7.9% (53 to 63 mmol/mol). Mean duration of diabetes in this trial was 10 years.[10] 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.[11] 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% CI 9% to 55%) in all-cause mortality associated with intensive metformin treatment in UKPDS 34.[8] 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).[10] 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-out.[12] Reductions in all-cause 2+

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).

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).[13] 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).[14] 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%).[9] The VADT reported reduction in microalbuminuria with absolute risk reduction (ARR) of 2.5% (p=0.05).[11] The UKPDS 33 showed a 25% relative risk reduction in aggregate microvascular endpoints (95% CI 7% to 40%).[7] 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 by 20% in risk of renal events (HR 0.80, 95% CI 0.72 to 0.88; p<0.0001) and eye events by 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; p=0.68).[15] 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, eg 10.5% *v* 3.5% for hypoglycaemia requiring medical assistance in the ACCORD trial (p<0.001),[10] 2.7% *v* 1.5% in the ADVANCE trial (HR 1.86, 95% CI 1.42 to 2.40).[9] UKPDS 33 showed a higher rate of major hypoglycaemia in patients on insulin or sulphonylureas than diet alone (insulin 1.8%, chlorpropamide 1.0%, glibenclamide 1.4%, diet 0.7%).[7] 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[10] (3 years)	3.5	0.4
ADVANCE[9] (median 5 years)	0.0	-1.0
UKPDS 33[7] (median 10 years)	5.6	2.5
UKPDS 34[8] (median 10.7 years)	Not specified	
VADT[11] (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 risk of microvascular disease and macrovascular disease. A target of 6.5%** (48 mmol/mol) **may be appropriate at diagnosis. Targets should be set for individuals in order to balance benefits with harms, in particular hypoglycaemia and weight gain.**

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-release and slow- or modified-release forms.

4.1 GLYCAEMIC CONTROL

4.1.1 GLYCAEMIC CONTROL COMPARED TO PLACEBO (OR DIET)

One systematic review (not updated since 2005) considered the effectiveness of metformin monotherapy compared with placebo or any active combination.[16] When compared with placebo, metformin showed more benefit for HbA1c (standardised mean difference, SMD -0.97, 95% CI -1.25 to -0.69), and FPG (SMD -0.87, 95% CI -1.13 to -0.61), but there were no significant differences for BMI or weight, total cholesterol, high-density lipoprotein (HDL) cholesterol, LDL cholesterol, triglycerides, or blood pressure. 1++

When compared with diet, metformin showed more benefit for HbA1c (SMD -1.06, 95% CI -1.89 to -0.22) and total cholesterol but no difference for 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 sulphonylureas have similar effects on HbA1c.[16,17] In the first, participants using metformin showed marginally larger reductions in HbA1c compared with those using sulphonylureas (SMD -0.14, 95% CI -0.28 to -0.01).[16] In the second, second generation sulphonylureas were associated with a trend towards greater HbA1c reduction than with metformin (SMD -0.09, 95% CI -0.30 to 0.10, not statistically significant).[17] There was no significant difference in HbA1c between those using metformin and those using insulin, meglitinides or alpha-glucosidase inhibitors.[16] 1++

A randomised controlled trial comparing combination therapy with metformin and canagliflozin to either as monotherapy in patients inadequately controlled by diet alone showed that canagliflozin was non-inferior to metformin (HbA1c (±SE) reduction of 1.42% (±0.07) and 1.37% (±0.07) (15.5 (±0.8) and 15 (±0.8) mmol/mol) with canagliflozin 300 mg and 100 mg doses, respectively; 1.30% (±0.07) (14.2 (±0.8) mmol/mol) with metformin monotherapy).[18] 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 (±0.7) mmol/mol) and -0.71% (±0.06) (-7.8 (±0.7) mmol/mol) for 1.5 mg and 0.75 mg doses respectively; -0.56% (±0.06) (-6.1 (±0.7) mmol/mol) with metformin.[19] A series of meta-analyses which incorporated 219 RCTs of glucose-lowering medications in people with type 2 diabetes (the AHRQ review) 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 studies.[2] 1++ 1+

4.2 HYPOGLYCAEMIA/WEIGHT GAIN/ADVERSE EFFECTS

The main adverse event reported more frequently with metformin compared with placebo in one systematic review was diarrhoea (absolute risk increase ARI 6.8%; RR 3.09, 95% CI 1.58 to 6.07). Hypoglycaemia was reported more frequently with metformin compared with diet (ARI 2.9%; RR 4.21, 95% CI 1.40 to 12.66).[16] 1++

Meta-analyses of RCTs of moderate to high quality involving comparisons of effects of metformin, sulphonylurea and thiazolidinedione monotherapies on weight (the AHRQ review) have favoured metformin by approximately -2.5 kg. Comparisons with DPP-4 inhibitors showed a smaller benefit (-1.3 kg, 95% CI -1.6 kg to -1.0 kg).[2] 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 canaglipfozin 100 mg; -1.8 kg (95% CI -2.4 kg to -1.1 kg) for canaglipfozin 300 mg),[18] while another study showed comparable weight loss with metformin monotherapy compared with dulaglutide.[19] 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.[20] 1++

4.3 CARDIOVASCULAR MORBIDITY AND MORTALITY

The UKPDS 34 allocated patients to either conventional (initial dietary modification with addition of a sulphonylurea for fasting plasma glucose >15 mmol/l) or a more intensive glycaemic control strategy (which could include metformin, sulphonylurea or insulin therapy). For overweight patients (54% with obesity), those allocated to metformin (n=342) had improved outcomes compared with those on conventional treatment (n=411), for any diabetes-related outcomes (RR 0.68, 95% CI 0.58 to 0.87), diabetes-related death (RR 0.58, 95% CI 0.37 to 0.91) and all-cause mortality (RR 0.64, 95% CI 0.45 to 0.91).[8] The metformin group also had a significantly reduced risk of myocardial infarction (RR 0.61, 95% CI 0.41 to 0.89). There were no significant differences between metformin and other comparison arms for other outcomes such as stroke, peripheral arterial disease and microvascular disease. 1++

Despite the benefits of metformin for overweight patients in comparison with a conventional treatment strategy, no benefits were observed for any of the above outcomes for comparisons between intensive treatment with metformin and intensive treatment with chlorpropamide, glibenclamide, or insulin (n=951).[8] 1++

Thus, while the evidence for clinically relevant outcome benefits with metformin is limited, the data remain some of the most robust available for pharmacological treatments of type 2 diabetes. They underpinned the recommendation in SIGN 116 of metformin as ‘first line’ oral therapy in people with type 2 diabetes, which is retained in the present update.

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. The drugs available are classed according to their date of release: first generation (acetohexamide, chlorpropamide, tolbutamide, tolazamide) and second generation (glipizide, gliclazide, glibenclamide (glyburide), gliquidone, glyclopyramide, glimepiride). First-generation agents are now rarely used in the UK.

5.1 GLYCAEMIC CONTROL

UKPDS 33 showed that the sulphonylureas chlorpropamide and glibenclamide were more effective at reducing HbA1c than diet alone.[7] Placebo comparator studies with newer sulphonylureas showed benefit in HbA1c but these were largely short duration trials of less than six months. One systematic review demonstrated a significant reduction in HbA1c with glibenclamide versus placebo.[21] | 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)*.[16,17] | 1++

Gliclazide MR and glimepiride were shown to be equally effective at reducing HbA1c at 27 weeks. HbA1c was not reduced further by glimepiride versus the longer established agent glibenclamide over 12–15 months.[22] | 1+

A meta-analysis of six short term studies including 1,364 patients suggested that sulphonylureas can achieve significant improvements in glycaemic control when added to metformin in patients who have inadequate glycaemic control.[23] | 1++

The NICE guideline on type 2 diabetes in adults recommends sulphonylureas as second- or third-line treatment after metformin, or as an alternative first-line treatment in those who cannot tolerate or have contraindications to metformin.[3] The AHRQ review reported no significant difference in effect on HbA1c between sulphonylureas and metformin, TZDs or DPP-4 inhibitors when used as monotherapy (*see Fig 7 in AHRQ review*). There was insufficient evidence to compare sulphonylureas with GLP-1 agonists. Results of meta-analyses of trials involving sulphonylureas in combination with metformin compared with other combinations did not favour sulphonylureas for HbA1c reduction.[2] | 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/ADVERSE EFFECTS

The UKPDS 33 showed a higher rate of major hypoglycaemia (defined as requiring third party help or medical intervention) in patients on sulphonylureas than diet alone *(see section 3.5)* and weight gain was greater (chlorpropamide 2.6 kg, glibenclamide 1.7 kg).[14] 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.[24] 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.[22] 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.[21] | 1+ 3

The AHRQ review identified 15 studies comparing sulphonylureas with metformin for incidence of hypoglycaemia *(see Fig 54 and Table 58 in AHRQ review)*. Five short-term RCTs were combined in meta-analysis, suggesting an increased risk of mild to moderate hypoglycemia with sulphonylureas compared with metformin (pooled OR, 2.59, 95% CI, 0.98 to 8.86). Nine studies were identified comparing TZDs with sulphonylureas of which | 1++

five were combined in meta-analysis (*see Fig 57 and Table 60 in AHRQ review)*. Risk of total hypoglycaemia was higher for sulphonylurea compared with TZD monotherapy (pooled OR 6.31, 95% CI, 4.08 to 9.76). Four RCTs were identified comparing sulphonylureas with DPP-4 inhibitors for hypoglycaemia (*see Table 62 in AHRQ review)*: these could not be combined in meta-analysis but DPP-4 inhibitors were favoured in all trials (range in OR 3.8 to 12.4). Five RCTs comparing sulphonylureas with GLP-1 agonists for hypoglycaemia could also not be combined in meta-analysis (*see Table 63 in AHRQ review)* but GLP-1 agonists were again favoured in all trials (range in OR 3.1 to 5.3).[2]

Given concerns about the risk of hypoglycaemia and weight gain with sulphonylureas, an RCT was conducted comparing alogliptin (25 mg) or 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.[25] 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).[26] 1-

An extension study to a 52-week double-blind RCT of once-daily canagliflozin 100 mg, canagliflozin 300 mg or glimepiride on a background of metformin monotherapy followed up participants to 104 weeks. Post hoc analysis showed that the proportion of participants which achieved reductions in both HbA1c and body weight at 104 weeks was 66%, 71%, and 27% with canagliflozin 100 and 300 mg and glimepiride, respectively. Odds for achieving this composite endpoint 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).[27] 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%).[28] Fewer than 3% of all hypoglycaemia events were nocturnal, but all of these occurred in those taking saxagliptin rather than placebo.[29] 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).[30] 1-

5.3 CARDIOVASCULAR MORBIDITY AND MORTALITY

The AHRQ review identified two high-quality RCTs and three retrospective cohort studies comparing metformin with sulphonylureas.[2] The first RCT, A Diabetes Outcome Progression trial (ADOPT) reported a non-significantly higher incidence of fatal 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 CVD adverse events over four years follow up with glibenclamide (26/1,441, 1.8%) than with metformin (46/1,454, 3.2%). Although 4,360 individuals were randomised, the study was not designed to examine cardiovascular disease and therefore had insufficient formal statistical power for this outcome. 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 of 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 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).
All three cohort studies higher risk reported a significantly higher risk of cardiovascular 1++

mortality for sulphonylurea versus metformin *(see Table 30 in AHRQ review).*[2]

In overweight participants of UKPDS 34 *(see sections 3 and 4.3)*, non-statistically significant trends were observed for rates of diabetes-related death, all-cause mortality, myocardial infarction and stroke to be higher for an intensive treatment strategy based on sulphonylureas or insulin than for an intensive treatment strategy based on metformin.[8] However, in comparisons of intensive treatment strategies versus conventional treatment by agents used for the seven major UKPDS outcomes, the only mean relative risk higher than unity was for stroke when treatment was based on sulphonylureas or insulin (RR 1.14, 95% CI 0.70 to 1.84, not statistically significant). 1++

There are two ongoing large RCTs that, on completion, will provide comparative evidence on the cardiovascular safety of sulphonylureas in relation to other agents.[31,32]

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

R **Sulphonylureas have potential for use as add-on second-line treatment to other oral therapies and may be useful in triple oral therapy.**

✓ Sulphonylurea therapy may be associated with weight gain and/or hypoglycaemia.

6 Thiazolidinediones

Thiazolidinediones (TZDs) 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 authority 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.[2,25,33,34] Combination therapy using doses of 15–30 mg daily have been shown to lower HbA1c by between 0.64 to 1.26% (6.99 to 13.77 mmol/mol).[35] | 1++

6.1.2 HYPOGLYCAEMIA/WEIGHT GAIN/ADVERSE EFFECTS

A systematic review of 18 RCTs with 11,565 participants providing loosely defined data on oedema reported a raised incidence with pioglitazone (RR 2.86, 95% CI 2.14 to 3.18).[36] This finding has been supported by other meta-analyses.[35,37-39] | 1++

Pioglitazone is associated with weight gain.[35] | 1++

One meta-analysis of five RCTs of duration one to four years reported fractures in 5.8% of women with type 2 diabetes treated with TZDs in comparison with 3.0% treated with other agents (OR 2.23, 95% CI 1.65 to 3.01). In this meta-analysis there was no increase in rates of fracture in men (OR 1.00, 95% CI 0.73 to 1.39).[40] 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).[41] 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).[42] | 1++ 2+ 3

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.[36] | 1++

A subgroup analysis from the PROactive trial suggested a reduction in fatal and non-fatal MI in the subgroup with previous myocardial infarction (n=2,445, HR 0.72, 95% CI 0.52 to 0.99, p=0.045; NNT=51 (95% CI 26 to 2,634).[43] In patients with previous stroke (n=984), subgroup analysis showed that pioglitazone reduced fatal or non-fatal stroke (HR 0.53, 95% CI 0.34 to 0.85, p=0.0085; NNT=21, 95% CI 12 to 75), while there was no effect on stroke risk in patients with no history of prior stroke (HR 1.06, 95% CI 0.73 to 1.52, p=0.767).[44] | 1+

However, a meta-analysis of 84 published and 10 unpublished trials of pioglitazone compared with placebo or other therapy, and excluding the PROactive trial, reported a reduction of all-cause mortality with pioglitazone (OR 0.30, 95% CI 0.14 to 0.63, p<0.05), but no significant effect on non-fatal coronary events.[45] 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).[46] | 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).[39] | 1+

These findings are corroborated by further data from a manufacturer-sponsored meta-analysis including 16,390 patients.[46] Serious heart failure was increased with pioglitazone (200 patients (2.3%) *v* 139 patients in control group (1.8%) (HR 1.41, 95% CI 1.14 to 1.76, | 1-

p=0.002).

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.[47] 1-

A study comparing pioglitazone to glibenclamide in patients with known grade II or III New York Heart Association (NYHA) functional class heart failure reported more hospitalisations with pioglitazone (9.9%) than glibenclamide (4.7%) but no difference in mortality.[48] 1+

R **Pioglitazone should be considered, usually as dual or triple therapy, for lowering HbA1c in combination with metformin, sulphonylureas, DPP-4 inhibitors or insulin.**

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, weight gain 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 MA for all rosiglitazone-containing medicines should be suspended across the European Union (EU). The MA 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 (http://tinyurl.com/Rosi2015).

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 (http://tinyurl.com/Rosi2015-FDA).

7 Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 inhibitors are oral agents which inhibit the activity of the enzyme DPP-4 and hence prolong the actions of endogenous Glucagon Like Peptide-1 (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.[49-51] These data include studies where DPP-4 inhibitors have been used as monotherapy compared with placebo,[49-51] dual therapy in combination with metformin, sulphonylurea or TZD compared with placebo[49-51] and for sitagliptin as triple therapy in combination with metformin and sulphonylurea.[52] The AHRQ review showed greater reduction in HbA1c with metformin (pooled between-group difference -0.4% (-4.37 mmol/mol), 95% CI -0.5% to -0.3% (-5.46 to -3.28 mmol/mol)).[2] However, there is some evidence from network meta-analysis of 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)).[3] — 1++ 4

The AHRQ review reported that in combination therapy, metformin and a DPP4 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 SGLT-2 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)). However, the authors note that their meta-analyses may have underestimated HbA1c reduction with the metformin and DPP-4 combination as some studies did not use optimal doses of comparator drugs.[2] — 1++

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.[3] — 4

When added in with background therapy of metformin and a sulphonylurea, sitagliptin provided less HbA1c reduction at 52 weeks than the SGLT-2 inhibitor canagliflozin. The latter also reduced weight and lowered blood pressure.[53] — 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%).[54] Similarly, pretreatment with sitagliptin prior to commencing basal insulin glargine provided superior glycaemic control despite lower insulin doses and fewer episodes of hypoglycaemia.[55] — 1+

7.2 HYPOGLYCAEMIA/WEIGHT GAIN/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 control groups.[50,56] In the AHRQ review, data from six RCTs favoured DPP-4 inhibitors over metformin for symptomatic hypoglycaemia (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 — 1++

sulphonylureas (range in OR 3.8 to 12.4) while a single RCT comparing DPP-4 inhibitors with SGLT-2 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).[2]

In combination therapy, the pooled odds ratio for mild or moderate hypoglycaemia across 27 RCTs comparing metformin and a DPP-4 inhibitor with metformin alone indicated a similar risk of hypoglycaemia (pooled OR 0.97, 95% CI 0.63 to 1.51).[2] 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). Moreover, one double-blind RCT comparing the DPP-4 inhibitor, sitagliptin (100 mg daily), with the SGLT-2 inhibitor, empagliflozin (10 mg and 25 mg daily) favoured 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 favoured DPP-4 inhibitors over TZDs (mean between-group difference of 2.3 kg and 2.5 kg. This was also the case for three RCTs which favoured DPP-4 inhibitors over sulphonylureas (range in mean between-group differences of 0.9 kg to 1.8 kg).[2] 1++

In keeping with these findings, weight gain was lower when metformin was combined with a DPP-4 inhibitor than with a TZD or SU. However, greater weight loss was observed with GLP-1 receptor agonists than with DPP-4 inhibitors when both were combined with metformin.[2]

Cases of pancreatitis were numerically (but not statistically) higher with DPP-4 inhibitors than with placebo in the large SAVOR-TIMI 53,[57] EXAMINE[58] and TECOS[59] 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%),[2] however, such reactions are uncommon. 1+ 1++

7.3 CARDIOVASCULAR MORBIDITY AND MORTALITY

Three major CV outcome trials of DPP-4 inhibitors compared with placebo and standard of care have been conducted to date (SAVOR-TIMI 53,[57] EXAMINE[58] and TECOS[59]).

All three met their predefined criteria for non-inferiority (ie safety) 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)[57] and there was a numerical (non-statistically significant) small excess of heart failure over 18 months with alogliptin *v* placebo in the EXAMINE trial.[60] However, 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).[59] 1+ 1++

R **DPP-4 inhibitors should be considered, usually as dual or triple therapy, for lowering HbA1c in combination with metformin, sulphonylureas, thiazolidinediones or insulin.**

8 Alpha-glucosidase inhibitors

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

The evidence for alpha-glucosidase inhibitors was obtained from three high quality systematic reviews[17,38,61] and one further RCT.[62] The majority of data reviewed examined alpha-glucosidase inhibitors as monotherapy in the management of patients with type 2 diabetes. Few studies were long term in determining the impact of a therapy for a chronic condition. The largest evidence base for the use of alpha-glucosidase inhibitors is with acarbose. There are no peer-reviewed data available on the long term effects of alpha-glucosidase inhibitors in terms of mortality, morbidity and quality of life.

A large cardiovascular outcome trial (n=6,526) of acarbose 50 mg three times per day versus placebo and standard of care in people with impaired glucose tolerance and known coronary artery disease is currently being conducted in China: it is expected to report in 2018.[63]

8.1 GLYCAEMIC CONTROL

Acarbose monotherapy reduces HbA1c when compared with placebo.[17,38,61] One meta-analysis reported lowering by 0.8% (8.7 mmol/mol) (95% CI 0.6 to 0.9% (6.6 to 9.8 mmol/mol), 28 comparisons) compared with placebo.[61] 1++

Alpha-glucosidase inhibitors inhibit postprandial glucose peaks thereby leading to decreased post load insulin levels especially when compared with sulphonylureas.[61] However, a small number of head-to-head trials and indirect data have shown that alpha-glucosidase inhibitors may be less efficacious in reducing haemoglobin HbA1c than other monotherapy regimens (acarbose versus sulphonylurea, absolute difference -0.75% (-8.20 mmol/mol), 95% CI -1.02 to- 0.48 (-11.15 to -5.25 mmol/mol)).[17] 1++

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

8.2 HYPOGLYCAEMIA/WEIGHT GAIN/ADVERSE EFFECTS

Compared with placebo, alpha-glucosidase inhibitors have minimal effects on body weight.[17,38,61] Abdominal discomfort (flatulence, diarrhoea and stomach ache) are the most frequently occurring adverse effects of alpha-glucosidase inhibitors and are dose related (acarbose ARI 25.8%, OR 3.3, 95% CI 2.3 to 4.7). As predicted from their mechanism of action, hypoglycaemic adverse effects do not occur.[61] The prevalence of gastrointestinal symptoms associated with acarbose (range, 15% to 30%) is similar to that with metformin and higher than that with thiazolidinediones or sulphonylureas (fewer than three trials for each comparison).[38] One RCT reported an incidence of 51% of patients reporting adverse events.[62] 1++ 1+

R **Acarbose should be considered for glycaemic control in people with type 2 diabetes.**

9 Glucagon like peptide-1 agonists

Glucagon Like Peptide (GLP)-1 is one of the key 'incretin' hormones - a group of rapidly metabolised peptides secreted from the gut in response to food which 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.GLP-1 also slows gastric emptying, resulting in slower absorption of glucose following meals, enhances satiety and reduces appetite. GLP-1 agonists mimic endogenous GLP-1 activity but are resistant to breakdown by the DPP-4 enzyme, resulting in prolonged action.

Five GLP-1 agonists are currently available, all in injectable formulations: albiglutide (once-weekly), 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 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 mcg twice daily) compared with placebo added to oral glucose-lowering agents (metformin and/or sulphonylurea) significantly reduced HbA1c (WMD for change in HbA1c from baseline -0.95% (-10.38 mmol/mol), 95% CI -1.21 to -0.7% (-13.22 to -7.65 mmol/mol)).[56] Those with a baseline HbA1c >9% (75 mmol/mol) had a larger reduction in HbA1c. 1++

Four placebo-controlled RCTs of 26 weeks duration reported in a meta-analysis demonstrated that in people with type 2 diabetes (disease duration 5–9 years, baseline BMI 30.0–33.5 kg 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)).[64] 1++

In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) study, which randomised 9,340 individuals at high cardiovascular risk who were taking one or more oral antidiabetic medicine (excluding DPP-4 inhibitors) to 1.8 mg of liraglutide or matching placebo once daily in addition to standard of care, mean HbA1c reduction at 36 months was -0.4% (4.37 mmol/mol) (95% CIs -0.45, to -0.34% (-4.92 to -3.72 mmol/mol)).[65] In the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial of lixisenatide compared with placebo and standard of care in 6,068 individuals with type 2 diabetes and a recent acute coronary syndrome (ACS), mean HbA1c reduction across all visits over 25 months was -0.27% (-2.95 mmol/mol) (95% CIs -0.31 to -0.22% (-3.39 to -2.40 mmol/mol)).[66] 1++

9.1.2 GLP-1 AGONIST COMPARED WITH SULPHONYLUREA OR TZD

In the evidence reviewed by NICE for first intensification of treatment, the combination of a GLP-1 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 was replaced by liraglutide at six months. By 12 months there were no significant differences in HbA1c reduction between the exenatide and metformin versus sulphonylurea and metformin combination.[3] A meta-analysis of two RCTs of 26 and 52 weeks duration, respectively, comparing liraglutide (1.2–1.8 mg once daily) with glimepiride (4–8 mg daily) reported no significant difference in HbA1c at study endpoint.[64] 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)).[67] 1++

9.1.3 GLP-1 AGONIST COMPARED WITH GLP-1 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 mcg twice daily reduced HbA1c by 0.79% (8.63 mmol/mol). The estimated treatment difference was -0.33% (-3.61 mmol/mol), (95% CI -0.47 to -0.18% (-5.14 to -1.97 mmol/mol), p<0.0001).[68] 1+

9.1.4 GLP-1 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)).[56] 1++

A further RCT of dulaglutide compared with insulin glargine (both in combination with prandial insulin) showed superiority of the GLP-1 agonist for HbA1c reduction 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.[69] Similarly, in those already on an optimal basal insulin the addition of once-weekly dulaglutide produced similar levels of HbA1c compared with the addition of prandial insulin lispro.[70] 1+

In a further RCT, participants were randomised to receive albiglutide (30 mg once weekly) or insulin glargine (10 U once daily) on a background of metformin and other therapy. At 52 weeks, HbA1c declined 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.[71] 1+

The NICE review concluded that a combination of metformin, a sulphonylurea and a GLP-1 agonist had similar effects on HbA1c to a combination of metformin and NPH insulin.[3] 4

9.1.5 COMBINATION THERAPY WITH GLP-1 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)).[72,73] 1++ 1+

Two RCTs have demonstrated that lixisenatide improves overall and postprandial hyperglycemia when added to insulin glargine. In the first RCT, 495 patients with established basal insulin therapy but inadequate glycaemic control were randomised to lixisenatide 20 mg 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 HbA1c <7% with lixisenatide (56% *v* 39%, p<0.0001).[74] 1++

In the second RCT, patients on dual oral antidiabetic medication involving any combination of metformin, sulphonylureas, glinides, 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 mg 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 1++

(-5.03 to -1.86 mmol/mol)) and a greater proportion of patients achieved target HbA1c with lixisenatide than with placebo (56% *v* 39%, p< 0.0001).[75]

At the time of writing, insulin glargine and lixisenatide in a once-daily single subcutaneous combination has received a marketing authorisation but has not been considered by SMC.

9.2 HYPOGLYCAEMIA/WEIGHT GAIN/ADVERSE EFFECTS

Severe hypoglycaemia was rare in exenatide and liraglutide studies and occurred only when sulphonylureas were co-prescribed.[64] Mild to moderate hypoglycaemia was seen in 16% versus 7% of patients treated with exenatide versus placebo (risk ratio 2.3; 95% CI 1.1 to 4.9).[56] In one study, 25.5% of patients treated with liraglutide versus 33.6% of patients treated with exenatide reported minor hypoglycaemia, p=0.01.[68] 1++ 1+

NICE and AHRQ reviews of GLP-1 agonists conclude that hypoglycaemia is less common with GLP-1 agonists compared with sulphonylureas when used either as monotherapy or in combination with basal or premixed insulin.[2,3] The evidence reviewed by by NICE indicated that although rates of hypoglycaemia were numerically lower with GLP-1 therapy compared with insulin, the difference was not statistically significant.[3] 1++ 4

GI adverse effects of GLP-1 agonists are directly related to their mechanism of action (delayed gastric emptying, central effects on satiety and appetite). The AHRQ review identified low quality evidence that GLP-1 agonists are associated with more GI adverse effects than metformin, sulphonylureas, TZDs or DPP-4 inhibitors. There is moderate strength evidence of higher rates of GI adverse effects with GLP-1 agonists in combination with metformin than with metformin alone and that the GLP-1 agonist and metformin combination causes more GI adverse effects than metformin in combination with sulphonylureas.[2] 1++

GLP-1 agonist treatment is associated with weight loss, eg 1.6 to 3.1 kg with exenatide over 24 to 52 weeks.[76-80] People with type 2 diabetes treated with exenatide 10 mcg twice daily versus liraglutide 1.8 mg once daily lost similar amounts of weight, -2.87 kg (SE, 0.33) versus -3.24 kg (SE 0.33), (estimated treatment difference -0.38 kg, 95% CI -0.99 to 0.23, p=0.22).[68] 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 group compared with all other therapies.[81] 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 GLP-1 agonist and placebo.[67] 1+ 1++

The combination of liraglutide and insulin degludec in patients on established oral glucose-lowering medication resulted in a significantly greater reduction in weight from baseline with the GLP-1 agonist (-2.7 kg) than with insulin degludec alone (0.0 kg), with similar rates of hypoglycaemia.[72] 1++

Two trials in which lixisenatide was added to insulin glargine for patients either established on basal insulin or newly titrated on basal insulin reported that reductions in body weight were greater with lixisenatide and main adverse events with lixisenatide were gastrointestinal.[74,75] 1++

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

9.3 CARDIOVASCULAR MORBIDITY AND MORTALITY

In the LEADER cardiovascular outcome trial (*see section 9.1.1*) 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. A limitation was 1++

significantly greater use of insulin and sulphonylureas and a consequent higher rate of hypoglycaemia in the placebo group which may have influenced event rates.[65]

A further large cardiovascular outcome trial (ELIXA, *see section 9.1.1*) demonstrated the cardiovascular safety (non-inferiority) of lixisenatide compared with placebo and standard of care over 25 months in individuals with type 2 diabetes and a recent ACS. There was no increase in pancreatitis or pancreatic neoplasm.[66] 1++

R **GLP-1 receptor agonist therapy should be considered in patients with a body mass index of ≥30 kg/m^2** (or ethnicity adjusted equivalent) **in combination with oral glucose-lowering drugs or basal insulin** (or both)**, when adequate glycaemic control has not been achieved with these drugs, or as an alternative to treatment with insulin in patients where treatment with metformin or sulphonylurea** (or both) **at maximally tolerated doses has been inadequate, and treatment with insulin would be the next option.**

10 Sodium Glucose Co-Transporter 2 inhibitors

Sodium glucose co-transporter 2 (SGLT-2) 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 ß-cell function. Three drugs are currently licensed in this class; canagliflozin, dapagliflozin and empagliflozin.

10.1 GLYCAEMIC CONTROL

10.1.1 MONOTHERAPY

A technology appraisal of SGLT-2 inhibitors as monotherapy identified three RCTs of daily treatment with dapagliflozin 10 mg. Dapaglifozin 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 with a greater reduction in individuals with 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% (64 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) and empagliflozin 25 mg by 0.86% (9.40 mmol/mol).[82] 1++

When combined in network meta-analysis, pooled results for all comparisons with placebo were consistent with the above *(see Table 2)*.[3] 4

Table 2: Network meta-analysis pairwise comparison of SGLT-2 inhibitor effect on HbA1c compared with placebo

Pairwise comparison	Mean difference in change from baseline HbA1c, % (mmol/mol) (95% credible interval)
Canagliflozin 300 mg	-1.19% (-13.01 mmol/mol) (-1.34 to -1.04% (-14.64 to -11.37 mmol/mol))
Canagliflozin 100 mg	-0.95% (-10.38 mmol/mol) (-1.06 to -0.84% (-11.58 to -9.18 mmol/mol))
Empagliflozin 25 mg	-0.88% (-9.62 mmol/mol) (-0.99 to -0.77% (-10.82 to -8.42 mmol/mol))
Empagliflozin 10 mg	-0.76% (-8.31 mmol/mol) (-0.87 to -0.65% (-9.51 to -7.10 mmol/mol))
Dapagliflozin 10 mg	-0.59% (-6.45 mmol/mol) (-0.70 to -0.48% (-7.65 to -5.25 mmol/mol)

For monotherapy comparisons with other agents, the AHRQ review reported no significant difference in HbA1c reduction between metformin and SGLT-2 inhibitor based on low-quality evidence. There was insufficient evidence available for all other monotherapy comparisons.[2] 1++

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 1+

(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).[83]

10.1.2 COMBINATION THERAPY

The combination of metformin with an SGLT-2 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)).[2] 1++

Two RCTs were identified which compared SGLT-2 inhibitors with sitagliptin when added in with other glucose-lowering agents. The first found that at week 52, a higher proportion of patients treated with canagliflozin than with sitagliptin achieved an HbA1c 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 in with metformin and a sulphonylurea. Moreover, a lower proportion had an HbA1c over 9% (75 mmol/mol) (1.9% *v* 8.5%; OR 0.18, 95% CI 0.08 to 0.43).[53] 1++

The second trial demonstrated that at week 52, when added to metformin, 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).[84] 1++

Several RCTs have compared SGLT-2 inhibitors with placebo in people receiving background insulin.[85-88]

In an extension study, 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 dapaglifozin 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 dapaglifozin group) compared with placebo added to insulin.[87] 1++

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)).[85] Another RCT 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 at 52 weeks.[86] 1++

10.2 HYPOGLYCAEMIA/WEIGHT GAIN/ADVERSE EFFECTS

As SGLT-2 inhibitors mediate their effects independently of insulin, there is a low risk of hypoglycaemia. The incidence of hypoglycaemia associated with SGLT-2 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 odds of any hypoglycaemia between metformin and SGLT-2 inhibitor monotherapy, although the direction of effect favoured SGLT-2 inhibitors in all trials (OR 0.46 (95% CI 0.16 to 1.30). 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 SGLT-2 inhibitor compared with metformin monotherapy of 1.74 (95% CI, 0.83, 3.66).[2] 1++

A meta-analysis of three RCTs assessing mild or total hypoglycaemia strongly favoured the combination of metformin plus an SGLT-2 inhibitor over metformin plus a sulphonylurea (OR 0.08, 95% CI 0.03 to 0.17).[2] 1++

A meta-analysis of five RCTs (12 to 78 weeks) showed no difference in rate of total hypoglycaemia between individuals randomised to metformin plus SGLT-2 inhibitor or metformin plus DPP-4 inhibitor (OR 0.98, 95% CI 0.06 to 15.84).[2] 1++

Two RCTs have reported a greater incidence of hypoglycaemia for canaglifozin when used in combination with insulin. One RCT found that more individuals treated with canagliflozin 100 and 300 mg than placebo had one or more documented hypoglycaemia episodes (33.8%, 36.5% and 17.9%, respectively) over 52 weeks of treatment.[89] 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).[86] 1++

The AHRQ review reported that SGLT-2 inhibitors are associated with a greater reduction in weight compared with metformin (-1.3 to -1.4 kg; three trials) or DDP-4 inhibitors (-2.5 to -2.7 kg; one trial) when used as monotherapy. Compared with metformin monotherapy, the combination of metformin plus an SGLT-2 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 SGLT-2 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).[2] 1++

A technology appraisal of SGLT-2 inhibitors as monotherapy compared effects of different drugs at different doses with placebo with direct and indirect comparisons. Results from the network meta-analysis are shown in Table 3.[82] 1++

Table 3: Network meta-analysis pairwise comparison of SGLT-2 inhibitor effect on weight compared with placebo

Pairwise comparison	**Mean difference in change from baseline weight,** kg (95% credible interval)
Canagliflozin 300 mg	-2.91 (-3.22 to -2.59)
Canagliflozin 100 mg	-2.02 (-2.41 to -1.65)
Empagliflozin 25 mg	-1.89 (-2.29 to -1.49)
Empagliflozin 10 mg	-1.74 (-2.15 to -1.33)
Dapagliflozin 10 mg	-1.58 (-2.01 to -1.14)

A reduction in body weight was also seen in studies comparing SGLT-2 inhibitors to placebo on background insulin. 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.[87] 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.[86] 1++

The most commonly reported adverse event in this class of drugs is genital mycotic infections. A meta-analysis of three medium- to high-quality, short RCTs compared metformin with SGLT-2 inhibitors and found more genital infections in those allocated to SGLT-2 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 to an SGLT-2 inhibitor in two trials. Both trials reported higher rates of genital infections among both women and men with SGLT-2 inhibitors compared with sitagliptin, with some of the comparisons statistically significant. In all comparisons involving SGLT-2 inhibitors used as combination therapy, the comparator was always favoured for incidence of genital mycotic infections.[2] 1++

There have been reports of diabetic ketoacidosis (DKA) associated with the use of SGLT-2 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).[90] SGLT-2 inhibitors should 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 abuse) or conditions that result in reduced oral intake or severe dehydration. SGLT-2 inhibitors should be stopped temporarily if undergoing major surgery or during serious illness.

10.3 CARDIOVASCULAR MORBIDITY AND MORTALITY

Following a prolonged period of uncertainty surrounding the safety of rosiglitazone between 2007 and 2015 *(see section 6.2)*, the EMA and FDA now require formal evaluation of CV risk via CV outcome trials prior to granting marketing authorisation for drugs used in the treatment of type 2 diabetes.[1] One CV outcome trial for SGLT-2 inhibitors (EMPA-REG) has published results. Several others are underway including CANVAS,[91] CREDENCE[92] and DECLARE-TIMI 58.[93]

There is currently insufficient evidence to combine in meta-analysis for the assessment of cardiovascular mortality and morbidity with SGLT-2 inhibitors.[2] 1++

The EMPA-REG trial was a double-blind RCT which investigated CV outcomes in patients with type 2 diabetes at high risk of CVD treated with empagliflozin (n=7,020). Participants received empagliflozin (10 or 25 mg) or placebo with continuation of standard of care treatment for diabetes and comorbid conditions. The primary outcome which was a composite of cardiovascular mortality, non-fatal MI and non-fatal stroke occurred in a significantly lower percentage of patients in the empagliflozin group than in the placebo group (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 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.[94] 1+

In the same trial there was a reduction with empagliflozin of a composite renal outcome comprising progression to microalbuminuria, doubling of serum creatinine, initiation of renal replacement therapy or death.[95] 1+

Until other CV outcome trials report *(see above)* it will not be known whether improvements in cardiovascular and renal outcomes are limited to empagliflozin or will be seen with other SGLT-2 inhibitors.

R **SGLT-2 inhibitors should be considered as an add-on therapy to metformin in patients with type 2 diabetes when hypoglycaemia is a concern or weight loss is considered to be potentially beneficial.**

R **In individuals with type 2 diabetes and established cardiovascular disease, SGLT-2 inhibition with proven cardiovascular benefit** (currently only empagliflozin) **are appropriate agents to add in with metformin.**

11 Insulin

When oral agents no longer provide effective glucose lowering, injectable therapy is required. In contrast to GLP-1 agonists, insulin is associated with weight gain and hypoglycaemia.[96] However, it provides effective glucose lowering for individuals for whom GLP-1 therapy is not indicated (BMI <30 kg/m^2), not tolerated (gastrointestinal adverse effects), or contraindicated (gall stones, medullary thyroid carcinoma). 1+

11.1 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.[97] 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 with standard of care in 12,357 people with prediabetes or type 2 diabetes over 6.2 years, indicates that continuing sulphonyurea therapy independently predicts both severe and non-severe hypoglycaemia.[98] 1++ 1+

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

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

When starting insulin therapy as a single injection before bedtime, NPH insulin is as effective in reducing HbA1c as basal insulin analogue therapy.[99-103] However, basal insulin analogue therapy is associated with fewer episodes of nocturnal and overall hypoglycaemia.[103,104] No difference was seen for severe hypoglycaemia. Collating evidence from six short-term trials, it was necessary to treat eight patients with type 2 diabetes (95% CI 6 to 11) with insulin glargine U100 compared with NPH (continuing oral agents) to avoid one episode of nocturnal hypoglycaemia.[105] Weight gain was slightly less with detemir than with NPH insulin when added to oral glucose-lowering agents (1 kg, 95% CI -1.69 to -0.23 kg).[106] 1++ 1+

More recently introduced longer-acting basal insulin analogues include insulin glargine U300 (300 units/ml, therefore 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,[107-109] and one moderate-quality 26-week extension study[110] of a 52-week RCT demonstrating lower rates of overall and nocturnal hypoglycaemia with insulin degludec compared with insulin glargine U100 (randomised 3:1).[111] 1+

A 2010 UK health technology assessment estimated the incremental cost effectiveness ratio (ICER) for use of glargine in place of NPH insulin for type 2 diabetes at £320,029; for detemir the equivalent estimate was £417,625.[103] 1++

U300 glargine was approved by SMC in 2015 on the basis of a similar cost to U100 glargine. Insulin degludec was approved by SMC in 2016 with insulin glargine as the comparator. The supporting cost-utility analysis reported short-term (one-year) incremental costs of £138 and incremental quality adjusted life year (QALY) gain of 0.0084 associated with insulin degludec compared with insulin glargine. The key clinical driver within the model was hypoglycaemic events. This yielded an ICER of £16,351 indicating insulin degludec was cost effective with respect to insulin glargine. However, in the light of changes to SMC policy, the falling costs of the comparator following the introduction of biosimilar insulin glargine (abasaglar) in 2015 will result in an increase in

the accompanying ICER.[112]

R **Once daily bedtime NPH insulin should be used when adding insulin to metformin. Basal insulin analogues should be considered according to level of concern regarding hypoglycaemia risk.**

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

11.3 INSULIN INITIATION AND INTENSIFICATION: BASAL VERSUS PRANDIAL VERSUS PREMIXED INSULINS

In the largest (n=708) and longest (three-year) randomised trial of complex insulin regimens to date ("4T"), three insulin initiation regimens (basal, prandial, and biphasic) were compared. The regimen was intensified (see below) after one year if necessary to achieve a target HbA1c of 6.5% (48 mmol/mol) (if HbA1c was unacceptably high this occurred earlier).[113]

The basal insulin group commenced bedtime insulin detemir (or twice daily dosing if required) with bolus mealtime insulin aspart added at intensification. The prandial group started with mealtime insulin aspart three times a day with subsequent intensification by addition of insulin detemir. The biphasic insulin group initially received twice daily biphasic insulin aspart, with later intensification by addition of insulin aspart at lunchtime.
At three years, the basal initiation regimen (moving to additional prandial insulin) resulted in the best combination of outcomes. HbA1c reduction was equivalent to either basal or prandial (6.9% (52 mmol/mol), 95% CI 6.6 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, 95% CI 1.08 to 1.34 *v* 0.86, 95% CI 0.71 to 1.01 u/kg/day). 1+

The AHRQ review identified five further trials which confirmed no difference in HbA1c lowering when biphasic insulin compared with basal insulin is 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.[2] 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.**

11.4 INTENSIFYING INSULIN THERAPY

11.4.1 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)).[114,115] However, the dose-titration algorithms used in nine of the 11 trials in one meta-analysis resulted in higher insulin doses being administered in those receiving premixed biphasic insulin preparations compared with basal insulin analogue therapy.[115] 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).[116] 1++ 1+

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

11.4.2 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.[115] 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.[99,117,118] 1+

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

12 Algorithm for glucose lowering in people with type 2 diabetes

NOT INCLUDED IN THIS VERSION

13 Provision of information

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

13.1 CHECKLIST FOR PROVISION OF INFORMATION

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive. The information contained in this section should be discussed with patients 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 convenient, and moreover is associated with increased concordance with therapy.

Principles

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

Metformin

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

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

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

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

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

Sulphonylureas

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

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

Individuals taking a short-acting sulphonylurea, eg gliclazide or glipizide who are fasting, for example during Ramadan, may be advised to take the largest dose with their evening meal and can halve their morning dose, if necessary. Longer-acting sulphonylureas such as glibenclamide and 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 and therefore the need, if possible, to avoid calorie excess.

Thiazolidinediones

People prescribed pioglitazone should be advised that they might experience ankle oedema. Where this occurs, discontinuation is usually appropriate. People taking pioglitazone should also be advised of the likelihood of weight gain and increased risk of fracture, although these are not necessarily reasons for discontinuation. No changes to pioglitazone regimens are required during Ramadan.

DPP-4 inhibitors

These newer 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, eg Ramadan.

GLP-1 agonists

These newer agents require to be injected subcutaneously, like insulin. 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 therapeutic response – weight and HbA1c.

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

GLP-1 agonists may be continued as usual for individuals who are fasting during Ramadan with multiple daily preprandial injections if meals are six hours or more apart. Otherwise, only a single injection should be taken before the sunset meal.

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

As for oral agents, people taking GLP-1 agonists may hold a regular (Group 1) driving licence without restriction.

Acarbose

When acarbose is prescribed, people with diabetes should be advised of the likelihood of gastrointestinal symptoms, particularly abdominal pain, diarrhoea and wind. These

symptoms mainly arise from the fermentation of undigested carbohydrates by colonic bacteria.

If acarbose if usually taken three times daily, the midday dose may be omitted or taken with the sunset meal in those who are fasting during Ramadan.

Insulin

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

- those who need assistance from a carer or healthcare professional to inject insulin and use of a long-acting insulin analogue (insulin detemir, insulin glargine) 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.

Rapid-acting analogues (whether as bolus insulin or as a component of pre-mixed insulin) may be appropriate in three specific groups:

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

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 affected. In general, drastic reductions in the total daily dose of insulin are not required. Many people with Type 2 diabetes are insulin resistant and will still require large doses. 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 should 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.

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 when switching back from once daily insulin glargine U300 to once daily insulin glargine U100.
https://www.medicines.org.uk/emc/medicine/30586 (accessed 24th February 2017)

SGLT-2 inhibitors

Individuals who are prescribed SGLT-2 inhibitors should be made aware of the risk of DKA 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.

There is a small risk of developing a urinary or genital yeast or fungal infection (eg thrush or balanitis) when taking SGLT-2 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 the diabetes treatment may need to be changed if these infections come back.

For those who are fasting, for example, during Ramadan, no changes in dose are required, although individuals taking SGLT-2 inhibitors should be reminded to stay adequately hydrated (at least 2 L water per day). If blood glucose is very high (>20 mmol/L) and rising, or if dehydrated, the SGLT-2 inhibitor should be stopped and urgent medical attention sought.

13.2 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 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.dft.gov.uk/dvla/medical.aspx

Healthtalk online
www.healthtalkonline.org

Healthtalk online is the website of the DIPEx charity. It provides access to people's experiences of living with diabetes.

My Diabetes My Way
www.mydiabetesmyway.scot.nhs.uk

NHSScotland interactive diabetes website to help support people who have diabetes and their family and friends. You'll find leaflets, videos, educational tools and games containing information about diabetes.

14 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.

14.1 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.

14.2 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

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

14.3 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:

NOT INCLUDED IN THIS DRAFT

14.4 HEALTH TECHNOLOGY ASSESSMENT ADVICE FOR NHSSCOTLAND

The Scottish Medicines Consortium has published advice on a range of drugs used in the management of people with diabetes. A summary of SMC advice for glucose-lowering agents in people with type 2 diabetes is published on the SIGN website.

15 The evidence base

15.1 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology using adaptations customised 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 Agency of Healthcare Research and Quality (AHRQ), of studies that assessed intermediate and clinical outcomes or safety for monotherapy or metformin-based combination therapy comparisons. 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. As this guideline represented an update to previous NICE guidelines the new version included a review of drug treatment to control blood glucose which conducted a systematic literature review of evidence 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, 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 include 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 SGLT-2 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. 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.

15.2 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:

NOT INCLUDED IN THIS DRAFT

16 Development of the guideline

16.1 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. Due to the limited remit the guideline development group was not fully multidisciplinary

16.2 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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16.2.1 ACKNOWLEDGEMENTS

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SIGN is also grateful to the following former members of the guideline development group

and others who have contributed to the development of the guideline.

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16.3 CONSULTATION AND PEER REVIEW

16.3.1 SPECIALIST REVIEWERS INVITED TO COMMENT ON THIS DRAFT

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16.3.2 PUBLIC CONSULTATION

The draft guideline was also available on the SIGN website for three weeks to allow all interested parties to comment.

Abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetes trial
ACS	acute coronary syndrome
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
CANVAS	CANagliflozin cardioVascular Assessment Study
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
DKA	diabetic ketoacidosis
DPP-4	dipeptidyl peptidase-4
eGFR	estimated glomerular filtration rate
ELIXA	Evaluation of Lixisenatide in Acute Coronary Syndrome trial
EMA	European Medicines Agency
EU	European Union
EXAMINE	EXamination of cArdiovascular outcoMes with alogliptIN versus standard of care trial
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GLP-1	Glucagon Like Peptide-1
GMC	General Medical Council
HbA1c	glycated haemoglobin
HDL	high-density lipoprotein
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
LDL	low-density lipoprotein
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results trial
MA	marketing authorisation

MR	modified release
MTA	Multiple Technology Appraisal
NICE	National Institute for Health and Care Excellence
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
QALY	quality adjusted life year
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
SGLT-2	sodium glucose co-transporter 2
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SMD	standardised mean difference
SPC	summary of product characteristics
SU	sulphonylurea
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?
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, 8	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 agonists affect mortality, cardiovascular morbidity and mortality, microvascular morbidity, HbA1c, weight, hypoglycaemia and other adverse events?
10	5	In adults with type 2 diabetes what is the evidence that SGLT-2 inhibitors affect mortality, cardiovascular morbidity and mortality, microvascular morbidity, HbA1c, weight, hypoglycaemia and other adverse events?
11	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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