

The management of type 2 diabetes: Newer oral hypoglycaemics and antidiabetic drugs

The National Institute for Health and Care Excellence (NICE) guidance on diabetes has recently been updated based on safety concerns, new evidence on newer oral antidiabetic therapies, new indications and licensed combinations for licensed class members and the potential impact of drugs coming off patent on health-economic issues.¹

In this bulletin we reinforce the current NICE recommendation to use metformin where appropriate as the first line treatment in patients requiring oral medication for type 2 diabetes. This bulletin also considers the role of modified release (MR) metformin and its combination products as well as the place in therapy of the newer antidiabetic drugs.

Recommendations

- Regularly discuss and (where appropriate) manage lifestyle interventions (e.g. stopping smoking, losing weight, taking more exercise) and control blood pressure. Refer patients to a structured education programme if available.¹
- When starting oral hypoglycaemic therapy, agree an individualised HbA1c target that is tailored to the patient's needs and circumstances. Take into account their personal preferences, comorbidities, risks from polypharmacy and their ability to benefit from long term interventions because of reduced life expectancy. Such an approach is especially important in the context of multimorbidity. Reassess the person's needs and circumstances at each review and think about whether to stop any medicines that are not effective.¹
- Support the person to achieve their agreed HbA1c levels. Measure HbA1c levels at 3 - 6 monthly intervals, as appropriate until HbA1c is stable then at six monthly intervals once stable. If the person achieves an HbA1c lower than target with no hypoglycaemia, encourage them to maintain it.¹
- Prescribe metformin (unless contra-indicated or not tolerated or a rapid response is required) as first line therapy for all new patients requiring medication; titrate the dose adequately to avoid metformin intolerance.¹
 - » Only consider a trial of modified release metformin if patients have persistent gastro-intestinal (GI) side effects despite the slow introduction of standard metformin formulation.¹
 - » Stop metformin if eGFR is below 30ml/minute/1.73m².
- A sulphonylurea, dipeptidyl peptidase-4 (DPP-4) inhibitor, pioglitazone or a sodium glucose cotransporter-2 inhibitor (SLGT-2) inhibitor (if a sulphonylurea or pioglitazone is not appropriate) can be considered for monotherapy, if metformin is contra-indicated or not tolerated.^{1,2}
- Base choice on effectiveness, safety (including hepatic and renal monitoring), tolerability, the person's individual circumstances, preferences, needs, available licensed indications and cost.
- For first and second intensification options see algorithm 1.
- If two drugs in the same class are appropriate, choose the option with the lowest acquisition cost.¹ See attachment 2 <https://www.prescqipp.info/resources/category/320-management-of-type-2-diabetes>

- Do not offer or continue pioglitazone if the person has heart failure or a history of heart failure, hepatic impairment, diabetic ketoacidosis, current or a history of bladder cancer, uninvestigated macroscopic haematuria. Review safety and efficacy every 3 - 6 months to ensure that only patients that are deriving benefit from pioglitazone continue to be treated.¹
- Glucagon-like peptide-1 mimetics (GLP-1s) are only recommended for triple therapy under specified circumstances if triple therapy with metformin and two other oral drugs is not effective, not tolerated or contraindicated.¹
- Only continue GLP-1 if HbA1C falls by at least 11mmol/mol (1%) and weight loss by at least 3% of initial body weight in six months.¹
- Only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant led multi-disciplinary team.¹
- Consider human NPH insulin as an option at second intensification if the person is still markedly hyperglycaemic (HbA1c rises to 7.5% (58mmol/mol) or other agreed level).
- Careful consideration should be given before prescribing a combination metformin/DPP-4 inhibitor product and these should only be used after dose titration on the separate component drugs and within licenced indications.
- Patients who are identified as not taking metformin with no documented clinical reason should be reviewed and restarted.
- Assess adherence with medicines and consider medicines optimisation in patients at all stages before initiating further medicines.

Background

Type 2 diabetes is a major public health issue. The prevalence of diabetes in England is 6% and around 90% of these people have type 2 diabetes; of these 90% are overweight or obese.^{1,3}

NICE guidance on type 2 diabetes in adults (NG28) was updated in December 2015. As before, the guidance advises adopting an individualised approach to diabetes care that takes into account patients' personal preferences, comorbidities, risks from polypharmacy, and their ability to benefit from long-term interventions because of reduced life expectancy. Such an approach is especially important in the context of multiple morbidity. Much of the evidence base used to inform the NICE guideline has been generated from studies involving younger adults (study mean ages ranged from 45 to 68 years). While the Guideline Development Group (GDG) thought that the recommendations are applicable to a wider age group, they highlighted that there needs to be a flexible approach to ensure that the care of older people with diabetes also addresses their broader health and social care needs.

NICE recommends a structured patient education approach to improve outcomes through addressing the individual's health beliefs, optimising metabolic control, addressing cardiovascular risk factors (helping to reduce the risk of complications), facilitating behaviour change (such as increased physical activity), improving quality of life and reducing depression. Updated guidelines re-iterate previous guidance that optimal blood pressure management and antiplatelet therapy is imperative in reducing cardiovascular adverse outcomes, blindness and renal failure.^{1,4} Lipid and hypertension guidance is not specifically dealt with in the NICE update, but is referred to.¹

NICE recommends an initial body weight loss of 5-10% be targeted in people that are overweight, while remembering that lesser degrees of weight loss may still be of benefit. Larger degrees of weight loss in the longer term will have an advantageous metabolic impact.¹ Many of these people will require oral medication as well as lifestyle advice.³

Blood glucose target measurements

Target HbA1c level should be agreed on an individual patient basis. Patients need to be encouraged to achieve the target and maintain it unless there are any resulting adverse effects (including hypoglycaemia), or their efforts to achieve their target, impair their quality of life.¹

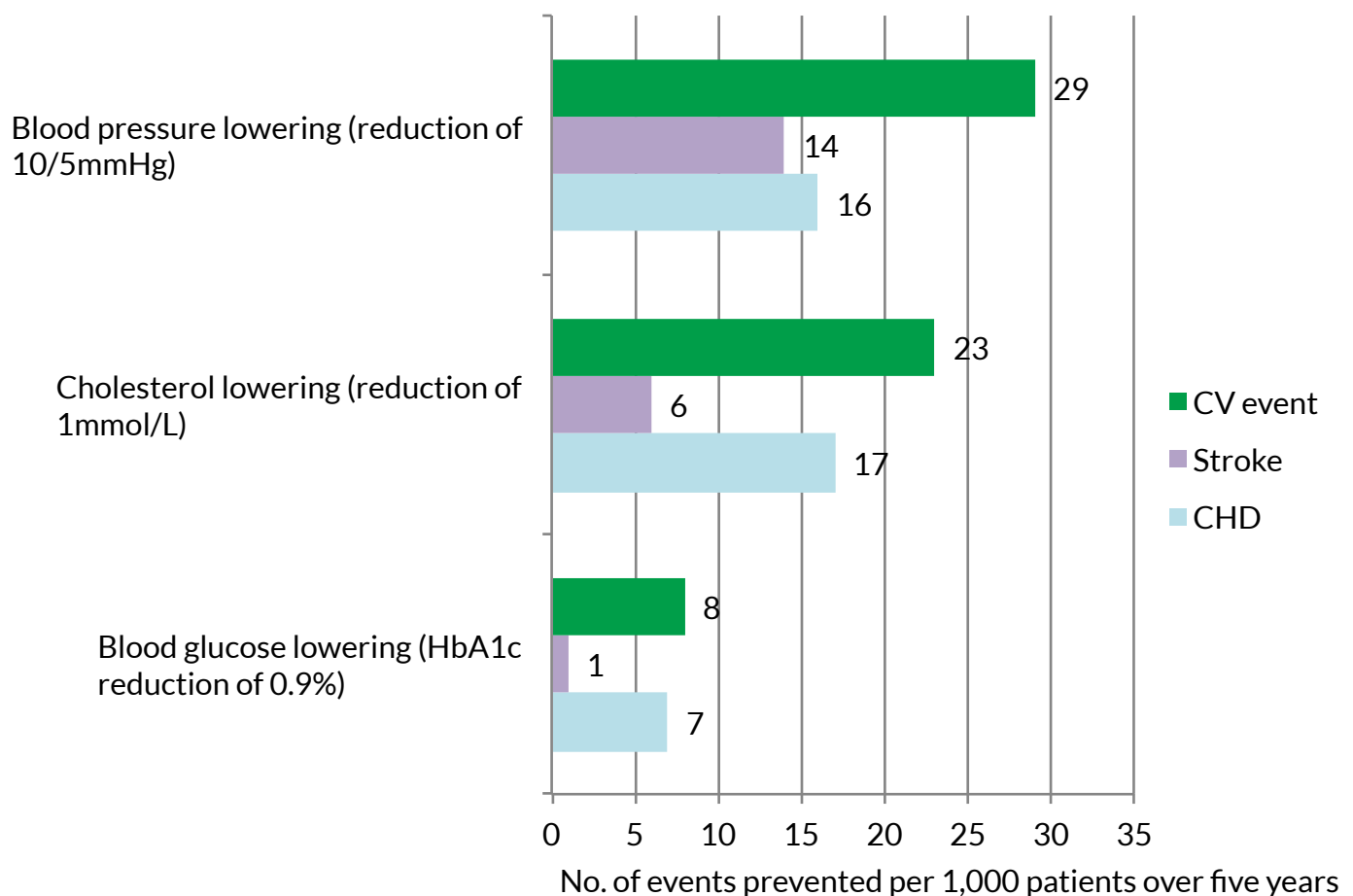
Key recommendations on blood glucose management from NG 28

Evidence for recommendations

Poor glucose control is associated with increased mortality^{5,6} and an increased risk of microvascular complications.^{1,7} NICE considered whether intensive strategies to lower target values are more effective than conventional strategies in achieving higher targets, in reducing long term complications. Intensive target levels are associated with increased risk of hypoglycaemia compared with conventional target levels.¹ Rising levels of HbA1c increase the risk of mortality and developing macrovascular and microvascular complications, with critical thresholds ranging from 42 to 53mmol/mol (6.0 to 7.0%). NICE could not provide guidance on HbA1c levels less than 42mmol/mol (6.0%), as only one very low quality study reported data for values ranging from 33 to 3 mmol/mol (5.2 to 5.8%).¹

NICE reviewed long term complications through population studies of low to high quality evidence. The GDG agreed that there is tentative evidence to suggest that intensive target levels may be beneficial in improving risks associated with mortality, macrovascular and microvascular complications compared with conventional target levels. They noted however that there was considerable heterogeneity in the target HbA1c levels used in the intensive control arms which ranged between 42mmol/mol (6.0%) or lower and less than 58mmol/mol (7.5%). There was also no restriction placed on which interventions could be used to achieve these targets. Both of these issues served to raise some doubt over the findings.¹ In addition, the GDG acknowledged that there was a statistically non-significant trend for increased risk of cardiovascular mortality and non-fatal stroke for people receiving intensive treatment compared with conventional strategies, but agreed that the findings were uncertain. This is in line with previous findings that blood glucose control appears to be less effective in reducing cardiovascular disease than controlling either blood pressure or blood lipids.^{7,8} Figure 1 illustrates that intensive blood glucose control is less effective at preventing co-morbidities than reducing cholesterol and blood pressure.

Figure 1: Relationship of reductions in cholesterol, blood pressure and HbA1c with improvements in coronary heart disease (CHD) and cardiovascular (CV) outcomes⁸⁻¹¹



While guidance on target values is important generally, the complexities of individual patient needs should predominate. In particular, special consideration of appropriate target values should be given to people at risk of hypoglycaemia, to achieve an acceptable balance between good glycaemic control and the likely negative impact on quality of life of this adverse event. Target levels may not be appropriate in:

- Renal failure.
- People for whom the target level may require increased medication that may cause adverse events or decreased medication compliance.
- People who would probably not benefit from the long-term impact on macrovascular and/or microvascular complications.

The GDG also stated that when agreeing target values with adults with type 2 diabetes, it is more important to examine the nature of the person's current medical condition, their complications and any other comorbidities rather than age alone.

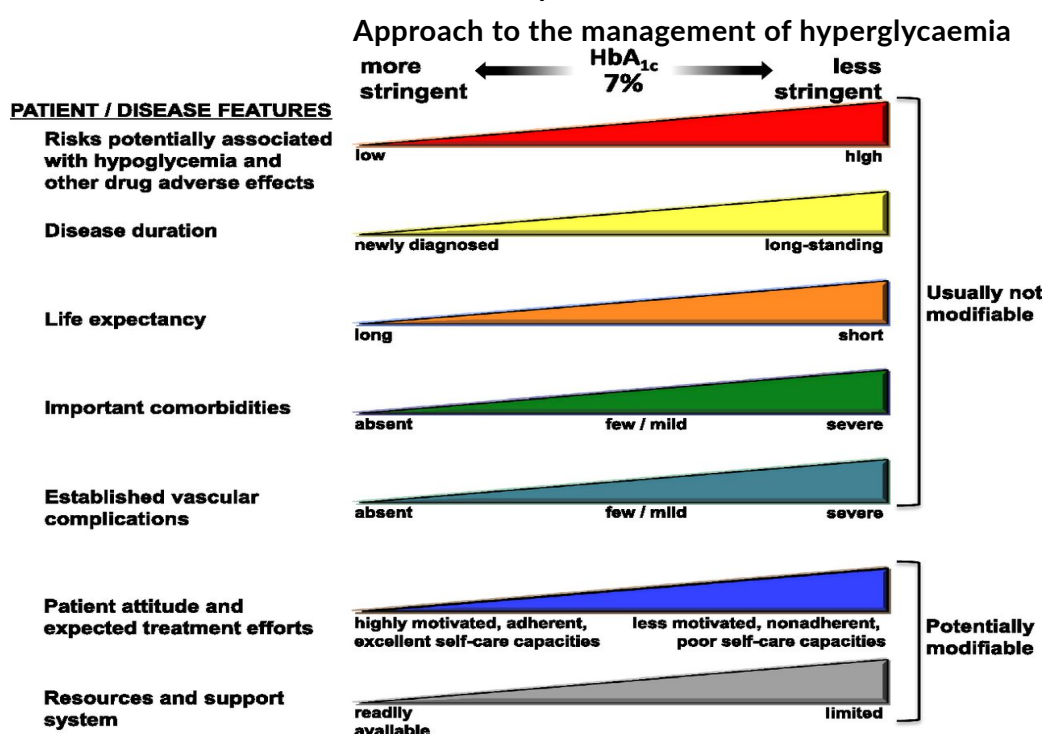
The Scottish Intercollegiate Guidelines Network (SIGN) Management of Diabetes Guidelines also suggests an HbA_{1c} target of 7.0% (53mmol/mol) for people with type 2 diabetes is reasonable to reduce risk of microvascular disease and macrovascular disease.¹²

QOF thresholds, which are set by NICE, have changed from the previous target of 53mmol/mol in 2009/10 to 59mol/mol from 2011/12 onwards.¹³

It should be re-emphasised that a holistic approach to an individual patient's care which includes deploying maximal lifestyle interventions (stopping smoking, losing weight, taking more exercise) should be considered. Good management of blood pressure (including the use of angiotensin-converting enzyme (ACE) inhibitors, calcium-channel blockers and diuretics) and blood lipid levels (including the use of statins and fibrates) can help to prevent or delay the onset of microvascular or macrovascular complications. (See NICE Clinical Guidance 181 and 127) This approach, along with taking metformin, seems likely to prevent more complications than a narrower focus on attempting to achieve intensive (rather than good) blood glucose control.

Figure 2 displays patient and disease characteristics that may influence HbA_{1c}. Thus, characteristics toward the left justify more stringent efforts to lower HbA_{1c}, whereas those toward the right suggest less stringent efforts. Where possible, such decisions should be made with the patient, reflecting his or her preferences, needs, and values.¹⁴

Figure 2: Patient and disease characteristics that may influence HbA_{1c}¹⁴



NICE has produced a Patient Decision Aid to help patients and clinicians discuss their options for controlling blood glucose. www.nice.org.uk/guidance/ng28/resources/patient-decision-aid-2187281197

Place in therapy for oral hypoglycaemic drugs and other antidiabetic drugs

The new guidelines denote the strength of the recommendation:

Offer – implies a strong recommendation, applicable to the vast majority of patients; the intervention will do more good than harm and will be cost effective.

Consider - denotes a weaker recommendation, when evidence of benefit is less certain. Whilst the intervention will do more good than harm for most patients and be cost effective, other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation. So the healthcare professional should spend more time considering and discussing the options with the patient.¹

Only metformin monotherapy is termed an 'offer' recommendation, i.e. a strong recommendation. Pioglitazone, DPP-4 inhibitors, GLP-1s and SGLT-2 inhibitors can be considered as dual therapy or triple therapy if specific criteria are met. To date research has largely focused on metformin-based combinations.

There is little evidence to guide management strategies on treatment combinations that do not include metformin. Randomised controlled trials and prospective longitudinal studies are needed to better understand the long-term efficacy and safety issues surrounding these medicines. Lately, regulatory authorities have issued guidance for evaluating the long-term cardiovascular (CV) safety of new anti-diabetes agents to ensure that CV safety is demonstrated with reasonable assurance.¹⁵⁻¹⁹

If an adult with type 2 diabetes presents with symptomatic hyperglycaemia, consider insulin or a sulphonylurea (i.e. rescue therapy). Review treatment when blood glucose control has been achieved.¹

A summary of the treatment pathway and differences in properties of anti-diabetic drug classes is provided in algorithm 1 (also attachment 1) and table 1, page 8-9.

Attachment 2 provide a summary of individual antidiabetic drug treatments, place in NICE guidance, prescribing notes, costs, licenced indications, initiation and discontinuation criteria where appropriate.¹

A further summary of the key differences in the different antidiabetic drugs is also provided in appendices 1-6, pages 12-18.

Monotherapy

Metformin - First line: refer to NICE guidance [NG28]¹

- Initiate metformin (start dose low and gradually increase over several weeks) if eGFR >45ml/min/1.73 m². Review the dose of metformin if eGFR is below 45 ml/min/1.73 m². Stop metformin if eGFR is below 30 ml/min/1.73 m². Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45 ml/min/1.73 m².¹
- Step up immediate release metformin dose over several weeks to minimise gastrointestinal effects.
- In a trial comparing immediate with modified release metformin, more diarrhoea, flatulence and abdominal pain were experienced in the modified-release group whilst more or equivalent proportions of patients, experienced nausea/vomiting, headache and dyspepsia/heartburn in immediate-release group (significance tests not performed). In placebo-controlled studies, patients on modified release metformin always experienced more gastro-intestinal (GI) adverse effects than those on placebo. A retrospective chart review found a significantly reduced frequency of GI adverse events in a cohort of patients when they were switched from immediate release to modified release. However, a cohort of patients taking metformin for the first time also experienced fewer GI adverse effects if they were commenced on modified release rather than the immediate-release formulation.²⁰⁻²³ NICE considered that the use of modified-release metformin preparations did not

reduce GI side effects in unselected patients. Differences in cost, and lack of other documented benefit, led to the conclusion that these therapies should be used only where gastrointestinal side effects related to the immediate-release preparation had been documented.¹

- Consider sulphonylureas, pioglitazone, DPP-4 inhibitors or an SGLT-2 inhibitor (if a sulphonylurea or pioglitazone is not appropriate as alternative first line agents if metformin is contra-indicated or not tolerated).^{1,2}
- Repaglinide is an alternative first line option as it is both clinically effective and cost effective in adults with type 2 diabetes. However, use may be constrained by the fact that it is presently only licensed in combination with metformin. This means that if repaglinide does not lead to optimal results as initial therapy, then there are no licensed options to intensify with another antihyperglycaemic medicine (see appendix 1, page 12).

First intensification of drug treatment (Dual therapy)¹

Only consider if HbA1c remains above 7.5% (58mmol/mol) or other higher agreed level

If HbA1c levels are not adequately controlled by a single drug and rise to 58 mmol/mol (7.5%) or higher, reinforce advice about diet, lifestyle and adherence to drug treatment and support the person to aim for an HbA1c level of 53mmol/mol (7.0%) and intensify drug treatment. Consider first intensification (dual therapy) as follows:

- Metformin and a DPP-4 inhibitor or,
- Metformin and pioglitazone or,
- Metformin and a sulphonylurea,¹
- Metformin and a SGLT-2 inhibitor may be appropriate for some people.

If metformin is contraindicated or not tolerated and initial drug treatment has not continued to control HbA1c to below the person's individually agreed threshold for intensification, consider dual therapy with:

- DPP-4 inhibitor and pioglitazone or,
- DPP-4 inhibitor and a sulphonylurea or,
- Pioglitazone and a sulphonylurea.¹ See cautions for pioglitazone in appendix 2, page 12.

Second intensification of therapy (Triple therapy)¹

Only consider if HbA1c remains above 7.5% (58mmol/mol) or other higher agreed level

If dual therapy with metformin and another oral drug has not continued to control HbA1c to below the person's individually agreed threshold for intensification, consider either triple therapy with:

- Metformin, a DPP-4 inhibitor and a sulphonylurea or pioglitazone or,
- Metformin, pioglitazone and a sulphonylurea or,
- Metformin, a SGLT-2i and a sulphonylurea or pioglitazone or,
- Starting insulin-based treatment.

If triple therapy with metformin and two other oral drugs is not effective, not tolerated or contraindicated, consider combination therapy with metformin, a sulphonylurea and a glucagon-like peptide-1 (GLP-1) mimetic. This recommendation is indicated within specific criteria as stated in appendix 5, page 14.

Note that GLP-1 mimetic therapy should only be continued if the person has had a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in six months).

If metformin is contraindicated or not tolerated, and if dual therapy with two oral drugs has not continued to control HbA1c to below the person's individually agreed threshold for intensification, consider insulin-based treatment.¹

Insulin treatment

Insulin treatment is an option at second intensification. When starting insulin therapy in adults with type 2 diabetes, use a structured programme employing active insulin dose titration that encompasses:

- Injection technique
- Continuing telephone support
- Self-monitoring
- Dose titration to target levels
- Dietary understanding
- DVLA guidance (at a glance guide to the current medical standards of fitness to drive)
- Management of hypoglycaemia
- Management of acute changes in plasma glucose control
- Support from an appropriately trained and experienced healthcare professional.¹

When insulin is initiated, metformin can be continued with insulin for people without contra-indications or intolerances.¹ Review the continued need for other blood glucose lowering agents.¹ In particular note MHRA cautions with pioglitazone as defined in appendix 2. No further agents are in the NICE treatment pathway as an add on after insulin has been started.

Use a structured programme to discuss benefits and risks of insulin treatment if other measures do not keep HbA1c to < 58 mmol/mol (7.5%) (or other agreed target).

The preferred third line agent is NPH insulin once or twice daily according to need. It can be given with a short acting insulin (particularly if HbA1c $\geq$ 75 mmol/mol [9.0%]) and administered either separately or as a biphasic human insulin (pre-mixed). It is important to note that targets need to be individualised (as noted above) according to the needs of the patient.

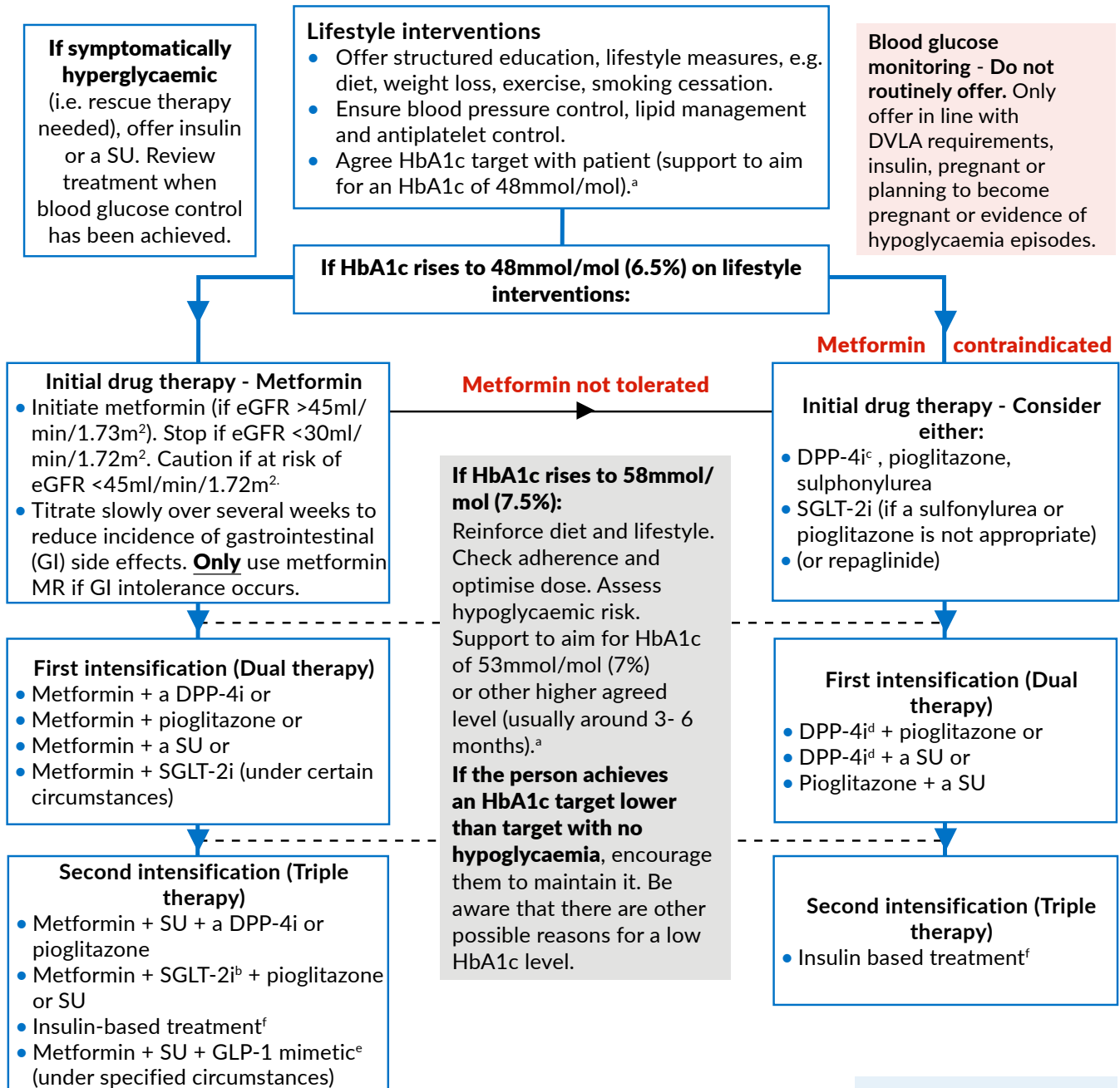
Insulin detemir or insulin glargine (but not degludec) may be considered if specific administration or lifestyle criteria are met.

Intensifying therapy may not be appropriate in all patients. If insulin is unacceptable or inappropriate because of employment, social, recreational or other personal issues, or obesity then consider agents as stated in the second intensification part of pathway – refer to algorithm 1.¹

Refer to PrescQIPP bulletins:

- Insulin analogues <https://www.prescqipp.info/insulin-analogues/category/95-insulin-analogues>
- Biosimilar insulin analogue <https://www.prescqipp.info/news/newsfeed/bulletin-130-launched-biosimilars-insulin-analogues>

Algorithm 1: Treatment algorithm for type 2 diabetes in adults¹



a. Agree an individualised HbA1c target based on: the person's needs and circumstances including preferences, comorbidities, risks from polypharmacy and tight blood glucose control and ability to achieve longer-term risk-reduction benefits. Consider relaxing the target HbA1c level as appropriate in people who are older or frail, people with reduced life expectancy, for people for whom tight blood glucose control poses a high risk, i.e. people at risk of falling, people who drive or operate machinery, people with significant co-morbidities. **b.** Only canagliflozin and empagliflozin are recommended as options in triple therapy regimens. The role of dapagliflozin in triple therapy will be reassessed by NICE in a partial update of NICE TA288. **c.** Alogliptin is not licensed as monotherapy. **d.** Linagliptin is not licensed as part of dual therapy with SU or pioglitazone. **e.** GLP-1s indicated if: BMI ≥ 35.0 kg/m² in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, or BMI < 35.0 kg/m², and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities. Continue GLP-1 therapy **ONLY** if at least 1% reduction in HbA1c and >3% initial body weight loss in 6 months. **f.** The preferred third line agent is NPH insulin once or twice daily according to need. Insulin detemir or insulin glargine (but not degludec) may be considered as alternatives if specific administration or lifestyle criteria are met.

DPP-4i – Dipeptidyl peptidase-4 inhibitor
GLP-1 – Glucagon like peptide-1 mimetic
SGLT2i – Sodium glucose cotransporter-2 inhibitor
SU– Sulphonylurea

NICE recommends drug treatment with the lowest acquisition cost if two drugs from the same class are appropriate. Ensure renal and hepatic monitoring for individual drugs.

Table 1: Properties of available glucose lowering agents.¹⁴ Refer to individual SPCs for further details

Class (or specific treatment in class)	Primary action	Advantages	Disadvantages	Cost/28 days ²⁴
Biguanides	↓ Hepatic glucose production	Extensive experience No Hypoglycaemia	Gastro-intestinal side effects Taste disturbance (rare) Lactic acidosis (very rare)	£3.48 to £8.52
Sulphonylureas	↑ Insulin secretion	Extensive experience	Hypoglycaemia ↑ Weight Ensure compliance with DVLA guidance	£0.99- £44.48 (however consider cost of blood glucose testing strips)
Meglitinides (Repaglinide)	↑ Insulin secretion	Dosing flexibility ↓ Post-prandial glucose excursions	Hypoglycaemia ↑ Weight Frequent dosing Only licensed with metformin	£5.90 to £10.99
Thiazolidinediones (Pioglitazone)	↑ Insulin sensitivity	No hypoglycaemia ↑ HDL ↓ Triglycerides	↑ Weight Avoid/cautions if current or history of bladder cancer, uninvestigated haematuria, fracture, history or current of heart failure, hepatic impairment	£10.12 to £30.46
DPP-4i	↑ Insulin secretion ↓ Glucagon secretion	Low risk hypoglycaemia Weight neutral	Acute pancreatitis Potential risk of heart failure in patients with existing heart or kidney disease	£26.60 to £33.26
SGLT-2i	By inhibiting SGLT2, reduces reabsorption of filtered glucose and lowers the renal threshold for glucose	Low risk hypoglycaemia ↓ Weight ↓ Blood pressure	Limited experience in > 75 years Avoid with volume depletion, loop diuretics, Genito-urinary infections Polyuria Rare reports of diabetic ketoacidosis including life threatening cases - test for ketones.	£36.59
GLP-1 mimetics	↑ Insulin secretion ↓ Glucagon secretion Slows gastric emptying ↑ Satiety	Low risk hypoglycaemia ↓ Weight	Gastro-intestinal side effects Acute pancreatitis Injectable Patient reluctance Training requirements	£54.14 to £109.87

Current spend (ePACT data February to April 2016)

The Information Centre report “Prescribing for diabetes in England: 2005/6 to 2014/15” found that the prescribing of antidiabetic drugs (including newer hypoglycaemic agents) has increased significantly in recent years.²³ The number of items prescribed increased by 74.1% (20.1 million) from 2005/6 to 2014/15 with a growth of net ingredient cost of 69% (£354.7million).

Across England and Wales, over £98 million is spent annually on metformin. An average of 54 % of all prescriptions for antidiabetic drugs were prescribed as metformin which accounts for 29% of the cost for antidiabetic drugs (ePACT February to April 2016).

If metformin achievement met the level the top 25th centile are achieving then the **potential savings would be over £13.7 million which equates to £22,632 per 100,000 patients.**

A significant proportion of costs in diabetes drugs is for the newer anti-diabetic drugs and there could be significant cost savings made across England and Wales by either switching to NICE recommended first line anti-diabetic treatments (metformin) if this has not been previously tried or discontinuing GLP-1s where they are not effective in line with NICE guidance.¹ Attachment 3 provides a data collection form for reviewing newer agents. A patient letter is provided in attachment 4 <https://www.prescqipp.info/resources/category/320-management-of-type-2-diabetes>

Savings/QIPP opportunities

Ensure that all doses are adjusted in renal or hepatic impairment.

Sulfonylureas

Review patients on glibenclamide which is a sulfonylurea associated with a higher risk of hypoglycaemia (especially in the elderly), also the 2.5mg tablet is currently Category A in the Drug Tariff and priced at £6.95 for 28.²⁴ Current annual spend across England and Wales is £243,140.

The current price for tolbutamide tablets is £11.12 for 28 x 500mg tablets.²⁴ The total spend on tolbutamide is currently over £1.3 million.

Modified release products

£45.5 million is spent annually across England and Wales on modified release metformin (forms 28% of all metformin prescribing).

- Over £7.5 million could be saved annually by switching 50% of metformin MR patients to immediate release metformin. This equates to £12,337 per 100,000 patients
- For immediate release gliclazide. See <https://www.prescqipp.info/resources/category/65-gliclazide>

DPP-4 inhibitors

If a DPP-4 inhibitor has met the NICE criteria, savings are available by switching from existing DPP-4 inhibitors products to alogliptin using strict criteria and follow up. See <https://www.prescqipp.info/alogliptin/category/125-alogliptin>

GLP-1 mimetics

Only use GLP-1s in triple therapy. Continue only if reduction in HbA1c of $\geq 1.0\%$ (11mmol/mol) AND 3% weight loss at six months.

Summary

- Offer metformin as first line treatment. Modified release metformin should only be considered where the immediate release preparation is not tolerated and treatment with metformin SR is thought to be beneficial to the patient.¹
- For first and second intensification options see algorithm 1. Base choice on effectiveness, safety (including hepatic and renal monitoring), tolerability, the person's individual circumstances, preferences, needs, available licensed indications and cost. If two drugs in the same class are appropriate, choose the option with the lowest acquisition cost.¹
- An individualised approach to blood glucose lowering is recommended. Support patients to aim for an optimal HbA1c of around 7.0% (53mmol/mol) at first and second intensification.¹
- Address maximal lifestyle interventions (stopping smoking, losing weight, taking more exercise) and control blood pressure before starting antidiabetic therapy to control symptoms and ensure lifestyle measures are regularly addressed with the patient.¹
- Review treatment with GLP-1 agents after six months. If there is no beneficial metabolic response then, consider stopping treatment and discussing a new HbA1c target with the patient or using NPH insulin where appropriate.¹

Appendix 1

Repaglinide [refer to NICE NG28]¹

- Repaglinide is a short-acting oral secretagogue indicated in adults with type 2 diabetes mellitus whose hyperglycaemia can no longer be controlled satisfactorily by diet, weight reduction and exercise. Repaglinide is also indicated in combination with metformin in adults with type 2 diabetes mellitus who are not satisfactorily controlled on metformin alone.^{1,25}
- Repaglinide is not widely used in current UK clinical practice. However NICE considered that given the consistent findings of significantly large clinically important reductions in HbA1c up to one year, healthcare professionals should be made aware of the available clinical and cost-effectiveness evidence supporting the use of this drug.¹
- Use may be constrained by the fact that it is presently only licensed in combination with metformin. This means that if repaglinide does not lead to optimal results as initial therapy, then there are no licensed options to intensify with another antihyperglycaemic medicine.¹
- The following substances may reduce the hypoglycaemic effect of repaglinide: oral contraceptives, rifampicin, barbiturates, carbamazepine, thiazides, corticosteroids, danazol, thyroid hormones and sympathomimetics.²⁵
- The following substances may enhance and/or prolong the hypoglycaemic effect of repaglinide: gemfibrozil, clarithromycin, itraconazole, ketokonazole, trimethoprim, ciclosporin, deferasirox, clopidogrel, other antidiabetic substances, monoamine oxidase inhibitors (MAOI), non-selective beta blocking substances, angiotensin converting enzyme (ACE)-inhibitors, salicylates, NSAIDs, octreotide, alcohol, and anabolic steroids.²⁵
- Repaglinide is principally metabolized via CYP3A4 and CYP2C8. Therefore, the manufacturer recommends that care should be taken when inhibitors or inducers of CYP3A4 and CYP2C8 are co-administered with repaglinide.²⁵
- The use of repaglinide might be associated with an increased incidence of acute coronary syndrome (e.g. myocardial infarction). However type 2 diabetes is also associated with an increased risk of cardiovascular disease.²⁵

Appendix 2

Sulfonylureas [refer to NICE NG28]¹

- A sulfonylurea, such as gliclazide, is an option in patients where metformin is not tolerated or contra-indicated, or where rapid response is required as a result of hyperglycaemic symptoms. Review treatment when blood glucose control has been achieved.
- Sulfonylureas may be considered as an option in dual therapy with metformin.¹ Consider substituting an alternative agent for the sulfonylurea if there is significant risk of hypoglycaemia (or its consequence) or a sulfonylurea is contraindicated or not tolerated. i.e. weight gain is an undesirable effect. Glibenclamide is associated with a greater risk of hypoglycaemia and should be avoided in the elderly.²⁶ Tolbutamide has an eleven times higher acquisition cost than gliclazide 80mg.²⁴
- Educate the patient about the risk of hypoglycaemia, as they are associated with an increased incidence of hypoglycaemia. In an observational study the annual risk for a first hypoglycaemia diagnosis associated with sulfonylurea use was 1.8% (1,800 per 100,000 person-years); long-acting formulations, renal impairment, older age, and incidental use of sulfonylureas were associated with a higher hypoglycaemia risk.²⁷ Although the evidence for selection of appropriate glycaemic targets in elderly patients is sparse, it is now acknowledged that prevention of hypoglycaemia must influence individualisation of treatment goals in this vulnerable group.^{1,28}
- Consider the risk of hypoglycaemia and DVLA requirements.²⁹
- A network meta-analysis (n=167,327) reviewed the risk of all-cause mortality, cardiovascular-related mortality, or myocardial infarction for sulphonylureas. Gliclazide and glimepiride were associated

with a lower risk of all-cause and cardiovascular-related mortality compared with glibenclamide.³⁰

- Modified release gliclazide should only be prescribed after careful consideration and where the use of modified release preparation is considered to be of benefit to the patient - see DROP-List bulletin: <https://www.prescripp.info/resources/category/65-gliclazide>
- Titrate over several weeks (as for metformin).

Appendix 3

Pioglitazone [refer to NICE NG28]¹

The marketing authorisation for rosiglitazone was withdrawn in 2010 by the European Medicines Agency who concluded that the benefits of rosiglitazone did not outweigh the increased cardiovascular risk.

- Do not offer or continue pioglitazone if the person has a heart failure or history of heart failure, hepatic impairment, diabetic ketoacidosis, current (or a history of) bladder cancer or uninvestigated macroscopic haematuria.¹
- In 2011, the MHRA reported that the use of pioglitazone was associated with a small increased risk of bladder cancer; in observational studies the relative risk ranged from 1.12 to 1.33 when diabetic patients receiving pioglitazone are compared with diabetic patients receiving other antidiabetic medicines but not exposed to pioglitazone. It was however concluded that the benefits continue to outweigh the risks for those who respond to treatment and in whom there are no identified risk factors for bladder cancer. Risk factors for the development of bladder cancer should be assessed.³¹
- Pioglitazone is contra-indicated in cardiac failure or history of cardiac failure (NYHA stages I to IV). When treating patients who have at least one risk factor for development of congestive heart failure (e.g. prior myocardial infarction or symptomatic coronary artery disease or the elderly), prescribers should start with the lowest available dose and increase the dose gradually. Patients should be observed for signs and symptoms of heart failure, weight gain or oedema; particularly those with reduced cardiac reserve.³² The MHRA guidance (2011) also notes that cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for the development of cardiac failure. It advises that if the combination is used, people should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac status occurs.^{1,31}
- MHRA guidance (2011) advises that '*prescribers should review the safety and efficacy of pioglitazone in individuals after 3 - 6 months of treatment to ensure that only patients who are deriving benefit continue to be treated*'.³¹ In light of age-related risks (especially bladder cancer, fractures and heart failure), the balance of benefits and risks should be considered carefully both before and during treatment in the elderly.³²
- The pioglitazone/metformin combination product (Competact®) is significantly more expensive than the two components prescribed separately.²⁴ Review all patients on this combination product.

Appendix 4

DPP-4 inhibitors (Gliptins) [refer to NICE NG28]¹

- Four of the currently available DPP-4 inhibitors (linagliptin, saxagliptin, sitagliptin and vildagliptin) are included in the review of updated NICE guideline (but not alogliptin, due to updated search restrictions of 2007 to June 2014), DPP-4 inhibitors are recommended as monotherapy if metformin is contraindicated or not tolerated. They are also recommended as dual therapy in combination with metformin or a sulphonylurea or as triple therapy in combination with metformin and a sulphonylurea.¹
- Review dosage in line with renal or liver impairment recommendations.
- The DPP-4 inhibitors are available as combination products with metformin, however these should only be considered once a patient is stabilised on a dose and treatment has been evaluated. The combination products are all fixed dose combination products and will therefore be inappropriate to

use in any patients stabilised on a different dose of metformin/ sulfonylurea. DPP-4 inhibitors have a flat pricing structure across strengths and therefore doses should be optimised to the fewest number of tablets taken.

- The Scottish Medicines Consortium has reviewed all five of the DPP-4/metformin combination products. They have accepted their restricted use in populations where the specific individual components are appropriate for the patient, and where the reduced pill burden would be beneficial to the patient, as this is at no extra cost to prescribing the DPP-4 alone.³³⁻³⁶
- MTRAC also reviewed the DPP-4 inhibitors. It noted that no significant differences were reported between the gliptins with respect to blood glucose-lowering efficacy against other oral diabetic treatments in the systematic review evidence, or in one RCT head-to-head comparison of sitagliptin and saxagliptin. This guidance summary recommends that, "if a gliptin is to be used, it is advised that the gliptin is selected based on the appropriate licensed indications, with the lowest acquisition cost".³⁷
- In terms of safety end points, the following outcomes have been reviewed. The cardiovascular safety of alogliptin has been evaluated in EXAMiNE; Over the follow-up period (median 18 months, N=5,380), alogliptin did not increase the risk of CV events (primary endpoint of composite death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke).¹⁶ Cardiovascular outcomes have also been studied with saxagliptin in the SAVOR-TIMI study (in 16,492 patients over 2.1 years). Saxagliptin did not increase or decrease the rate of ischemic events, though the rate of hospitalisation for heart failure was increased. The authors concluded that although saxagliptin improves glycaemic control, other approaches are necessary to reduce cardiovascular risk in patients with diabetes.¹⁷ A further study, TECOS, will evaluate the effects of adding sitagliptin to usual diabetes care on cardiovascular outcomes and clinical safety.¹⁸
- A recent US Food and Drug Administration safety review reported that saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease. The recommendation is that health care professionals should consider discontinuing saxagliptin and alogliptin in patients who develop heart failure and monitor their diabetes control.³⁸
- Alogliptin is a DPP-4 inhibitor licensed for dual and triple therapy. Alogliptin as add-on therapy reduces HbA1c by around 5.5mmol/mol (0.5%) compared with placebo in both dual and triple therapy.³⁹ However there is no data comparing alogliptin with other DPP-4 inhibitors. The SMC and All Wales Medical Strategy Group (AWSMG) has accepted alogliptin for restricted use in dual therapy only.^{40,41} Alogliptin is priced 16-20% lower than existing DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin and linagliptin).²⁴ Guidance on reviewing DPP-4 inhibitors to alogliptin in selected patients only is provided in the PrescQIPP alogliptin bulletin which is available at: <http://www.prescqipp.info/resources/viewcategory/267-alogliptin>

Appendix 5

Glucagon-like peptide-1 (GLP-1) mimetics:¹ [refer to NICE NG28]. Technology appraisals for exenatide prolonged release suspension (TA248) and liraglutide (TA203) have been superseded by NG28.

The currently licensed GLP-1 agonists are exenatide (Byetta®), exenatide once weekly (Bydureon®), liraglutide (Victoza®), lixisenatide (Lyxumia®), albiglutide (Eperzan) and dulaglutide (Trulicity®).

Exenatide ER, dulaglutide and albiglutide are once weekly preparations.

Exenatide, liraglutide and lixisenatide are included in the review of the update of the NICE guideline.¹

Recommendations

- The updated NICE guidance now only recommends a GLP-1 for triple therapy when metformin and two other oral drugs are not effective, not tolerated or contraindicated. GLP-1s can be considered in

combination with metformin, and a sulfonylurea for adults with type 2 diabetes who:

- » Have a BMI of 35 kg/m² or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or
- » Have a BMI lower than 35kg/m² and:
 - » For whom insulin therapy would have significant occupational implications or
 - » Weight loss would benefit other significant obesity-related comorbidities.¹
- Co-prescribing with insulin should only be with specialist advice and ongoing support from a consultant-led multidisciplinary team.¹
- SIGN 116 emphasises the need to apply careful clinical judgement in those people with a long duration of type 2 diabetes on established oral glucose-lowering drugs with poor glycaemic control (>10 years) as these individuals are poorly represented in published studies, to ensure insulin therapy is not delayed inappropriately for the perceived benefits of GLP-1 mimetics.¹² The commonest side effects are related to gastrointestinal upset with nausea being reported most commonly.²⁶
- There has been concern about the possibility of an increase in the incidence of acute pancreatitis. The Association of British Clinical Diabetologists (ABCD) have assessed the current evidence on GLP-1 mimetics and pancreatic damage and have concluded that at this time there is insufficient information to modify current recommendations.⁴² It is still recommended to advise patients that they should stop taking GLP-1 therapy if they experience continued severe abdominal pain and seek medical assistance.
- Exenatide and exenatide once weekly: Standard release exenatide injection (Byetta®) is administered twice a day and may be unsuitable/less cost effective for those patients requiring a carer or district nurse to administer their medicines as this would mean two daily visits for administration. If changing from standard release to modified release (once weekly dose):^{43,44}
 - » Patients may experience a transient increase in blood glucose.
 - » The dose of sulfonylurea may need to be reduced.
 - » Effects of modified release exenatide may continue for ten weeks after discontinuation.

Lixisenatide was launched in the UK in March 2013. The NICE evidence summary concluded that *“GetGoal-Mono does not provide evidence relevant to the proposed licensed indications for the drug. GetGoal-L-Asia provides some evidence but there are questions over its relevance to the UK population.”*⁴⁵

- Dulaglutide is the second once weekly GLP-1 (and fifth GLP-1 mimetic) to be launched in the UK. Dulaglutide once weekly, when added to metformin, was statistically superior to exenatide twice daily (both in combination with pioglitazone), statistically superior to sitagliptin and statistically non-inferior to liraglutide 1.8mg daily. As with the other glucagon-like peptide-1 (GLP-1) receptor agonists there are limited data from randomised controlled trials (RCTs) on the effect of dulaglutide on patient-oriented outcomes, such as rates of macrovascular or microvascular events, or on long-term safety.⁴⁶
- Albiglutide is the fifth GLP-1 agonist to be licensed in the UK for the treatment of diabetes and the third once-weekly formulation. There is no experience in patients with NYHA class III-IV cardiac failure. Albiglutide has not been studied in combination with prandial insulin, dipeptidyl peptidase-4 (DPP-4 inhibitors), or sodium/glucose cotransporter 2 (SGLT-2) inhibitors.⁴⁷
- Albiglutide is the only GLP-1 that has a monotherapy licence. There is limited experience of albiglutide when combined with sulphonylureas and thiazolidinediones, and metformin and sulphonylureas and thiazolidinediones.⁴⁶ In direct comparative studies, albiglutide was superior to glimepiride and sitagliptin. It was inferior to pioglitazone and liraglutide 1.8mg.^{48,49}

Appendix 6

Sodium–glucose co-transporter 2 (SGLT-2) inhibitors – see NG28¹

Additional technologies

Dapagliflozin – refer to NICE TA 288;⁵⁰ Canagliflozin – refer to NICE TA 315;⁵¹ Empagliflozin – refer to NICE TA 336;⁵² Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes – refer to NICE TA 390.²

Sodium–glucose co-transporter 2 (SGLT-2) inhibitors block the reabsorption of glucose in the kidneys and promotes excretion of excess glucose in the urine. NICE technology appraisals cover dapagliflozin, canagliflozin and empagliflozin.^{49–51}

NICE NG28 states that SGLT-2 inhibitors '*may be appropriate for some people*' as an option for dual or triple therapy or in combination with insulin according to the relevant technology appraisals.^{1,50–52}

- No direct head to head studies comparing efficacy or safety within the class currently exist. The most commonly encountered adverse effects experienced include: hypotension, genital and/or urinary tract infections (more common in women and people with a prior history), volume depletion particularly in patients over 65 years of age, an elevation in haematocrit and increased incidence of hypoglycaemia dependent upon background therapy (normally seen with insulin or insulin secretagogues).^{50–52}
- Empagliflozin is the third SGLT-2 inhibitor launched onto the UK market. Empagliflozin as add-on therapy to metformin plus a sulfonylurea, or to pioglitazone with or without metformin, reduces HbA1c by about 6 mmol/mol (0.5–0.6% points) compared with placebo over 24 weeks (two randomised controlled trials [RCTs] of dual or triple therapy). No serious safety concerns have been identified so far; however, there are no long-term safety data and no data on the effect on empagliflozin on the long-term complications of type 2 diabetes.⁵³
- Longer-term efficacy and safety of the SGLT-2 inhibitors has not been established.
- Diabetic ketoacidosis has been recently reviewed by the European Medicines Agency (EMA) to be a rare adverse reaction (affecting up to 1 in 1,000 patients) of SGLT-2 inhibitors. If diabetic ketoacidosis is suspected or confirmed (including in patients with risk factors of DKA), treatment with SGLT-2 inhibitors should be stopped immediately and should not be re-started unless another cause for the ketoacidosis is identified and resolved.⁵⁴ Patients who may be at higher risk of DKA include patients with a low beta-cell function reserve (e.g. type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse. SGLT-2 inhibitors should be used with caution in these patients.^{55–57} The EMA highlights that the benefits of SGLT-2 inhibitors continue to outweigh the risks in the treatment of type 2 diabetes.⁵⁴
- In April 2016, the EMA issued guidance of a review of canagliflozin after an increase in amputations, mostly affecting the toes, observed in the CANVAS trial. The Pharmacovigilance Risk Assessment Committee may also extend the scope of the review to include other SGLT-2 inhibitors.⁵⁸ A drug safety update has been issued for healthcare professionals reminding them about the importance of routine foot care to avoid cuts or sores of the feet and to treat them promptly should they occur to prevent infection and ulceration. Patients at increased risk of amputation (such as those who have had a previous amputation) should be carefully monitored. As a precautionary measure, HCPs may consider stopping treatment with canagliflozin in patients who develop lower limb complications (e.g. skin ulcer, osteomyelitis, or gangrene), at least until the condition has resolved, and continue to monitor the patient closely).⁵⁹
- None of the three SGLT-2 inhibitors should be initiated in patients with an eGFR < 60 mL/min/1.73m². Monitoring of renal function is recommended for all three SGLT-2 inhibitors as per their respective SPCs.^{55–57} See attachment 2 for specific requirements (add link).

- A recent FDA communication has strengthened the existing warning about the risk of acute kidney injury for canagliflozin and dapagliflozin. Healthcare professionals are advised to consider factors that may predispose patients to acute kidney injury prior to starting them on canagliflozin or dapagliflozin. These include decreased blood volume; chronic kidney insufficiency; congestive heart failure; and taking other medications such as diuretics, blood pressure medicines called angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), and nonsteroidal anti-inflammatory drugs (NSAIDs). Assess kidney function prior to starting canagliflozin or dapagliflozin and monitor periodically thereafter. If acute kidney injury occurs, promptly discontinue the drug and treat the kidney impairment.⁶⁰
- The SPC for dapagliflozin states that while a causal relationship between dapagliflozin and bladder cancer is unlikely, as a precautionary measure, dapagliflozin is not recommended for use in patients concomitantly treated with pioglitazone.⁵⁵
- NICE recommends dapagliflozin, canagliflozin and empagliflozin as part of dual therapy with metformin only if a sulphonylurea is contraindicated or not tolerated or the person is at significant risk of hypoglycaemia or its consequences.^{1,50-52}
- NICE recommends dapagliflozin, canagliflozin, and empagliflozin in combination with insulin with or without other antidiabetic drugs.⁵⁰⁻⁵²
- Canagliflozin and empagliflozin are recommended as part of triple therapy with metformin and a sulphonylurea or metformin and pioglitazone. Dapagliflozin is only recommended in combination with metformin and a sulphonylurea unless as part of a clinical trial.^{1,50-52}
- NICE now recommends canagliflozin, dapagliflozin and empagliflozin as monotherapies when metformin is contraindicated or not tolerated and when diet and exercise alone do not provide adequate glycaemic control, only if a DPP-4 inhibitor would otherwise be prescribed and a sulphonylurea or pioglitazone is not appropriate.²
- A further publication of dapagliflozin in triple therapy regimens is expected January 2017 and will partially update TA288 dapagliflozin in combination therapy for treating type 2 diabetes.⁶¹

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Additional PrescQIPP resources



Briefing



Data pack



Audit, patient letters, algorithms



Available here: <https://www.prescqipp.info/resources/category/320-management-of-type-2-diabetes>

Information compiled by Anita Hunjan, PrescQIPP Programme, July 2016 and reviewed by Katie Taylor, Senior Medicines Evidence Reviewer, August 2016.

Non-subscriber publication December 2016.

Contact help@prescqipp.info with any queries or comments related to the content of this document.

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