PrescQIPP
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Type 2 diabetes in adults

In England, Scotland and Wales approximately £922 million annually is spent on the prescribing of antidiabetic drugs (NHSBSA Aug-Oct 22) and Public Health Scotland Aug-Oct 22).

This bulletin looks at the care and management for adults (aged 18 and over) with type 2 diabetes in-line with guidance from the National Institute for Health and Care Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN). It focuses on education, dietary advice, managing cardiovascular risk, managing blood glucose levels, and identifying and managing long-term complications. Along with the associated support materials listed at the end of the bulletin, it provides advice and support to assist a range of primary care health professionals including GPs, nurses and pharmacists to improve the care of people with type 2 diabetes. Cost savings are illustrated for organisations considering undertaking a diabetes medicines optimisation project.

Recommendations

- A structured education programme should be offered at the time of diagnosis, with annual reinforcement and review.
- Individualised lifestyle interventions (dietary advice, weight loss, exercise, alcohol consumption and smoking status) should be regularly discussed and integrated in a personalised diabetes management plan.
- Target HbA1c levels should be agreed on an individual basis and people need to be encouraged and supported to achieve the target and maintain it. Measure HbA1c levels every three to six months until stable, then measure HbA1c six monthly.
- Do not routinely offer self-monitoring of capillary blood glucose (SMBG) to adults with type 2 diabetes, unless in-line with NICE guideline [NG28].
- Intermittently Scanned Continuous Glucose Monitoring (isCGM) can be offered to adults with type 2 diabetes on multiple daily insulin injections who:
  - Have recurrent hypoglycaemia or severe hypoglycaemia.
  - Have impaired hypoglycaemia awareness.
  - Have a condition or disability (including a learning disability or cognitive impairment) that means they cannot self-monitor their blood glucose by capillary blood glucose monitoring but could use an isCGM device (or have it scanned for them).
  - Would otherwise be advised to self-measure at least eight times a day.
- When starting oral hypoglycaemic therapy, base choice on effectiveness, safety, tolerability, monitoring requirements, licensed indications, cost, individual clinical circumstances, preferences and needs.
- Assess cardiovascular status to determine whether the person with type 2 diabetes has chronic heart failure, established atherosclerotic cardiovascular disease or is at high risk of developing cardiovascular disease. Refer to the NICE guideline on cardiovascular disease: risk assessment and reduction, including lipid modification.

Recommendations

- Treat in-line with NICE guideline [NG28] for first line drug treatment and if needed, further treatment options summarised in algorithm 1.
- Review people prescribed metformin:
  - If estimated glomerular filtration rate (eGFR) is below 30mL/minute/1.73m^2 stop metformin.
  - If the eGFR is below 45mL/minute/1.73m^2 review metformin dose and adjust as appropriate.
  - If prescribed modified-release metformin with no documented gastrointestinal side effects, consider a switch to standard-release metformin where appropriate.
  - Check vitamin B12 levels in patients who have symptoms suggestive of vitamin B12 deficiency. Consider periodically monitoring patients with risk factors for vitamin B12 deficiency.
- If two drugs in the same class are appropriate, choose the option with the lowest acquisition cost.
- Review pioglitazone prescribing to ensure it is not prescribed in people with:
  - Heart failure or history of heart failure.
  - Hepatic impairment.
  - Diabetic ketoacidosis.
  - Current, or a history of, bladder cancer.
  - Uninvestigated macroscopic haematuria.
  - Review safety and efficacy every three to six months to ensure that only patients that are deriving benefit from pioglitazone continue to be treated.
- Glucagon-like peptide-1 (GLP-1) receptor agonists:
  - Should only be continued if the person has had a reduction of at least 11mmol/mol [1.0%] in HbA1c and weight loss of at least 3% of initial body weight in six months.
  - Should only be offered in combination therapy with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team.
- Combination products should only be considered once a patient is stabilised as they are all fixed dose products. Check the price as some can be less costly, the same price or more expensive than prescribing the single components.
- When starting an insulin for which a biosimilar is available, use the product with the lowest acquisition cost, that is suitable for the individual, this will usually be the biosimilar.

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Background

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood sugar. Hyperglycaemia, or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems including the heart, blood vessels, eyes, kidneys, and nerves. Diabetes is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation. Type 2 diabetes (formerly called non-insulin-dependent, or adult-onset) results from the body's ineffective use of insulin.[1]

There are currently 4.9 million people living with diabetes in the UK, with 850,000 with undiagnosed type 2 diabetes. Approximately 90% of people with diabetes have type 2 diabetes.[2,3] 2019 data derived from the GP quality and outcomes framework in England, Wales and Northern Ireland and the Scottish Diabetes Survey and published by Diabetes UK, showed an increase in the number of people living with a diabetes diagnosis in the UK of more than 100,000 compared to the previous year. At this rate the number of people with diabetes, including the undiagnosed population, is expected to rise to 5.3 million by 2025.[2] Early diagnosis is vital as complications can begin five to six years before some people are diagnosed with type 2 diabetes.[3] People with type 2 diabetes have a reduced life expectancy by an average of up to ten years.[4] Health impacts and complications of diabetes includes:[1,4]

- A two to three-fold increased risk of heart attacks and strokes.
- Reduced blood flow and neuropathy in the feet increases the chance of foot ulcers, infection and eventually the need for limb amputation.
- Diabetic retinopathy – an important cause of blindness which occurs as a result of long-term accumulated damage to the small blood vessels in the retina. Close to one million people are blind due to diabetes.
- Kidney failure – diabetes is among the leading causes of kidney failure.

Table 1: Risk factors for diabetes[2,4]

Risk factor	Additional information
Obesity and inactivity	• Especially central obesity. • Overeating and inactivity can exacerbate insulin resistance. • Obesity accounts for 80–85% of the overall risk for developing type 2 diabetes
Family history	• People with a family history of diabetes are two to six times more likely to have diabetes. • The risk of developing diabetes if one parent has type 2 diabetes is about 15%. • The risk of developing diabetes if both parents have type 2 diabetes is about 75%.
Ethnicity	• People of African-Caribbean, Black African or South Asian descent are 2-4 times more likely to develop type 2 diabetes than white people.
Gestational diabetes	• Women with a history of gestational diabetes have a seven-fold increased risk for developing type 2 diabetes later in life. • Children born to mothers with gestational diabetes have a six-fold increased risk for developing type 2 diabetes.
Diet	• A low-fibre, high glycaemic index (GI) diet may increase the risk of being overweight or obese. • High-GI foods contain carbohydrates that are broken down quickly and cause a rapid increase in blood glucose levels.
Drug treatments	• Statins, corticosteroids, and combined treatment with a thiazide diuretic plus a beta-blocker, can increase the risk for developing hyperglycaemia and type 2 diabetes.
Polycystic ovary syndrome	• This increases the risk of non-diabetic hyperglycaemia and type 2 diabetes.
Metabolic syndrome	• Insulin resistance is commonly associated with the metabolic syndrome. • Metabolic syndrome is defined as a combination of raised blood pressure, dyslipidaemia, fatty liver disease, central obesity, and a tendency to develop thrombosis.
Low birth weight for gestational age	• There is some evidence that preterm birth before 35 weeks of gestation is associated with an increased risk for type 2 diabetes developing in adult.
Age	• Risk increases with age.

Cardiovascular disease (CVD) including stroke and peripheral arterial disease (PAD) is the leading cause of death in people with type 2 diabetes. There is a two-fold increased risk of stroke within the first five years of diagnosis compared with the general population and people with type 2 diabetes are 2.5 times more likely to have a myocardial infarction and develop heart failure than people without diabetes. PAD is a risk factor for the development of diabetic foot disease and foot ulcers and is present in up to 50% of people with diabetic foot ulcer. Diabetes is the commonest cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD), which may require renal replacement therapy or kidney transplantation.[4]

Statistics from NHS Business Services Authority (NHSBSA) states that 57.9 million drugs items used in diabetes were prescribed in England during 2020/21, at a cost of £1.2 billion. This represents 12.5% of the total spend on all prescription items prescribed in England.[5]

National guidance

NICE guideline [NG28] covers the care and management of adults (aged 18 and over) with type 2 diabetes. It focuses on education, dietary advice, managing cardiovascular risk, managing blood glucose levels, and identifying and managing long-term complications, for example CKD. In March 2022, NICE reviewed the evidence and made new recommendations on the use of continuous glucose monitoring (CGM) in type 2 diabetes.[6]

NICE has several other guidelines relevant to people with diabetes:

- NICE guideline [NG17] - Type 1 diabetes in adults: diagnosis and management.
- NICE guideline [NG3] - Diabetes in pregnancy: management from preconception to the postnatal period.
- NICE guideline [NG18] - Diabetes (type 1 and type 2) in children and young people: diagnosis and management.

The SIGN clinical guideline 154 focuses on pharmacological management of glycaemic control in people with type 2 diabetes. It provides evidence-based recommendations and best practice guidance on:[7]

- Optimal targets for glucose control for the prevention of microvascular and macrovascular complications.
- The risks and benefits of the principal therapeutic classes of glucose-lowering agents and insulins currently available.

However, lifestyle interventions, including appropriate diet, physical activity, blood glucose monitoring and other behaviours are vital to self-management in people with type 2 diabetes, but these were not included in the remit of this guideline.[7]

SIGN have also published recommendations based on current evidence for best practice in the management of both type 1 and type 2 diabetes. SIGN guideline 116 management of diabetes includes lifestyle interventions and recommendations for the management of cardiovascular, kidney and foot diseases.[8]

SIGN also have several guidelines in development relating to diabetes, which are due to be published from 2023 onwards:[9]

- Diabetes in pregnancy (due August 2023).
- Type 1 diabetes (due October 2024).
- Type 2 diabetes prevention (due September 2024).

Management of type 2 diabetes

NICE guideline, NG28 recommends adopting an individualised approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes, taking into account their personal

preferences, comorbidities and risks from polypharmacy, and their likelihood of benefiting from long-term interventions. Such an approach is especially important in the context of multimorbidity.[6]

Education

A structured education programme based upon adult learning theories is an integral part of diabetes care, and this should be explained and offered to all adults with type 2 diabetes and their family members or carers (as appropriate) at the time of diagnosis, with annual reinforcement and review.[6,8]

The program should be evidence-based and have specific aims and learning objectives and supports the person and their family members and carers to develop attitudes, beliefs, knowledge and skills to self-manage diabetes. It should have a structured curriculum and be delivered by trained and competent educators. The programme should be quality assured, be reviewed by trained, competent, independent assessors and be assessed against key criteria to ensure sustained consistency.[6,8]

Group education programmes are the preferred option, but if people are unable or prefer not to take part in group education they should be provided with an alternative of equal standard.[6] One such programme, known as DESMOND (Diabetes Education and Self-Management for Ongoing and Newly Diagnosed), was developed by several NHS organisations and delivers high quality education to people with type 2 diabetes, or those who are at risk of diabetes.[10] It involves activities for groups of ten, with individuals able to speak to an educator. It aims to make the diabetic patient an expert and empowered to make their own decisions.[10]

Structured education programmes for people with type 2 diabetes show variable effects on glycaemic control. Research in this area is difficult to carry out and does not lend itself well to traditional randomised controlled intervention trials. The lack of head-to-head comparative trials renders it impossible to recommend one specific programme over any other. Most education interventions are associated with some HbA1c improvement but this is not a universal finding. HbA1c changes vary with the interventions used but, where benefit is seen, the magnitude of change is usually in the range of 3 to 11mmol/mol (0.3 to 1.0%) improvement. In a multicentre (207 GP practices across 13 primary care sites in the UK), cluster randomised controlled trial, involving 894 patients, the DESMOND programme did not lead to improvement in HbA1c after 12 months but was associated with around 1kg greater weight loss and 5% less cigarette smoking.[8]

Dietary and lifestyle advice

Provide dietary advice in a form sensitive to the person's needs, culture and beliefs, willingness to change, and the effects on their quality of life. Individualised and ongoing nutritional advice should be provided by a healthcare professional with specific expertise and competencies in nutrition. Dietary advice and other lifestyle modifications such as increasing physical activity and losing weight should be integrated in a personalised diabetes management plan. People with type 2 diabetes should be encouraged to follow the same healthy eating advice as the general population, which includes:[6]

- Eating high-fibre, low-glycaemic-index sources of carbohydrate, such as fruit, vegetables, wholegrains and pulses.
- Choosing low-fat dairy products.
- Eating oily fish.
- Controlling their intake of saturated and trans fatty acids.

Adults with type 2 diabetes should be discouraged from using foods marketed specifically for people with diabetes.[6]

For people that are overweight NICE recommends an initial body weight loss of 5-10%, 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.[6]

Obese adults with type 2 diabetes should be offered individualised interventions to encourage weight loss (including lifestyle, pharmacological or surgical interventions) in order to improve metabolic control.[8] Assessment for bariatric surgery should be offered to people with a BMI of 35 or over and considered for people with a BMI of 30 to 34.9 who have recent-onset type 2 diabetes as long as they are also receiving or will receive assessment in a tier three weight service (or equivalent). Assessment should also be considered for people of Asian family origin who have recent-onset type 2 diabetes at a lower BMI than other populations as long as they are also receiving or will receive assessment in a tier 3 weight service (or equivalent).[11]

In addition to healthy eating and losing weight people with type 2 diabetes should be advised to stop smoking and increase their level of physical activity. Patients with diabetes can drink alcohol in moderation as part of a healthy lifestyle, however recommendations and advice should be individualised.[6,8] There is evidence that drinking two to three units of alcohol is not associated with hypoglycaemia in people with type 1 or type 2 diabetes. Observational evidence suggests a protective effect of alcohol consumption for vascular endpoints including death in patients with type 2 diabetes. However, acute alcohol consumption reduces hypoglycaemia awareness. All patients with diabetes should be aware of the high calorific value of alcohol and the implications of excess consumption on body weight.[8]

Management of other risk factors for increased cardiovascular mortality and morbidity, such as hypertension and lipid modification should be reviewed and treatment optimised.[4]

Hypertension is positively related to the risk of CVD death, with a progressive increase in risk with rising systolic pressures. Each 10mm Hg reduction in systolic pressure is associated with a 15% (95% CI 12 to 18%) reduction in the risk of CVD death over ten years.[8] The diagnosis, treatment and monitoring of hypertension is broadly the same for people with type 2 diabetes as for other people.[6] NICE guideline [NG136] - Hypertension in adults: diagnosis and management includes information on identifying and treating primary hypertension in people aged 18 and over, including people with type 2 diabetes. It aims to reduce the risk of cardiovascular problems such as heart attacks and strokes by helping healthcare professionals to diagnose hypertension accurately and treat it effectively.[23]

Patients without established CVD, should be offered atorvastatin 20mg once daily for primary prevention if any of the following apply:

- Aged 84 years and younger, and their estimated 10-year risk of developing CVD is 10% or more.
- 85 years of age or older, taking into account the person's preferences, benefits and risks of treatment, and co-morbidities (including frailty and multimorbidity).
- Chronic kidney disease (CKD).

Type 2 diabetics with established CVD should be offered 80mg atorvastatin once daily for secondary prevention of CVD. Aim for a greater than 40% reduction in non-HDL cholesterol.[4]

Do not offer antiplatelet therapy (aspirin or clopidogrel) to adults with type 2 diabetes without CVD. For further guidance on the primary and secondary prevention of CVD in adults with type 2 diabetes, see the NICE guidelines on cardiovascular disease [CG181] and acute coronary syndromes [NG185].

Blood glucose monitoring

HbA1c

Glycated haemoglobin (HbA1c) reflects average plasma glucose over the previous two to three months in a single measure which can be performed at any time of the day and does not require any special preparation such as fasting. This has made it a key measure for assessing glycaemic control in people with established diabetes.[8]

Individualised HbA1c target should be discussed and agreed with adults with type 2 diabetes. They

should be encouraged to reach their 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. The NICE patient decision aid on agreeing HbA1c targets, can be used to support these discussions.[6]

HbA1c levels should be measured every three to six months (tailored to individual needs) until HbA1c is stable on unchanging therapy. Then six months once the HbA1c level and blood glucose lowering therapy are stable.[6] HbA1c should be interpreted with caution in people with abnormal red blood cell turnover or abnormal haemoglobin type, e.g. severe anaemia, chronic renal disease.[4]

Support the person to aim for an HbA1c level of:[6]

- 48mmol/mol (6.5%) when managed either by lifestyle and diet or by lifestyle and diet combined with a single drug not associated with hypoglycaemia.
- 53mmol/mol (7.0%) for adults on a drug associated with hypoglycaemia.
- If HbA1c rises to 58mmol/mol (7.5%) on single drug treatment, reinforce lifestyle, diet and adherence to drug treatment advice and intensify drug treatment aiming for 53mmol/mol (7%).

SIGN guidance recommends that a HbA1c target of 53mmol/mol (7.0%) among people with type 2 diabetes is reasonable to reduce the risk of microvascular and macrovascular disease. A target of 48mmol/mol (6.5%) may be appropriate at diagnosis. Targets should be set with individuals to balance benefits with harms, in particular hypoglycaemia and weight gain.[7]

Consider relaxing the target HbA1c level on a case-by-case basis with particular consideration for people who are older and frailer if:[6]

- They are unlikely to achieve longer-term risk-reduction benefits, for example, people with a reduced life expectancy.
- Tight glycaemic control would put them at increased risk, for instance they:
  - Are at risk of falling.
  - Have impaired awareness of hypoglycaemia.
  - Drive or operate machinery as part of their job and for whom tight blood glucose control would not be appropriate.
- Intensive management would not be appropriate, for example, if they have significant comorbidities.

The European Society of Cardiology and the European Association for the Study of Diabetes, have also issued collaborative guidance which states that less stringent HbA1c goals, e.g. 64mmol/mol (<8%) or 75mmol/mol (≤9%) may be adequate for elderly people with long-standing diabetes and limited life expectancy, and frailty with multiple comorbidities, including hypoglycaemic episodes.[12]

The Association of British Clinical Diabetologists (ABCD) position statement on managing frailty and associated comorbidities in older adults with diabetes, define frailty, diagnosis and assessment methods and sets out the following recommendations:[13]

- Prescribed glucose-lowering medications should have a low risk of hypoglycaemia, minor side effects profile and be cost-effective.
- 'Start low and go slow' when titrating medication in frail older adults.
- The glycaemic goal should be individualised based on comorbid medical conditions in addition to cognitive and functional status.
- In mild to moderate frail older adults, an HbA1c target of 53-64mmol/mol (7-8%) is appropriate depending on self care management abilities and the presence of additional risk factors.
- In severe frailty an HbA1c target of 59–69mmol/mol (7.5-8.5%) is more protective.
- Many frail older adults have medical conditions that interfere with HbA1c measurements. In such cases, focus on random blood glucose targets at 6.7–11.1mmol/L throughout the day instead of HbA1c targets.

Self-monitoring of capillary blood glucose

NICE does not recommend routinely offering self-monitoring of capillary blood glucose (SMBG) in addition to HbA1c for adults with type 2 diabetes unless:[6]

- The person is on insulin.
- There is evidence of hypoglycaemic episodes.
- The person is on oral medication that may increase their risk of hypoglycaemia while driving or operating machinery.
- The person is pregnant or is planning to become pregnant .

Short term SMBG may be necessary when starting or stopping oral or intravenous corticosteroids or to confirm suspected hypoglycaemia.[6]

Intermittently scanned continuous glucose monitoring (isCGM)

The NICE committee responsible for the scoping and reviewing the evidence suggested that studies identified during routine surveillance of evidence for continuous glucose monitoring (CGM) for type 2 diabetes should be reviewed to ascertain the effectiveness of real time CGM (rtCGM) and intermittently scanned continuous glucose monitoring (isCGM – commonly known as flash) versus SMBG techniques. Also to consider whether routine rtCGM or isCGM use is now more appropriate for certain populations of people with diabetes.[14] The NICE committee discussed how CGM could potentially be useful for many people with type 2 diabetes. Examples from current practice in which adults who have insulin-treated type 2 diabetes and use isCGM have had good outcomes were also collated and considered. Because of the additional cost associated with CGM and the large number of adults with type 2 diabetes, the committee used both the evidence and their clinical experience to decide who would gain the most benefit from using isCGM.[14]

The NICE guideline recommends offering isCGM also known as “flash glucose monitoring” to adults with type 2 diabetes on multiple daily insulin injections, if any of the following apply:[6]

- They have recurrent hypoglycaemia or severe hypoglycaemia.
- They have impaired hypoglycaemia awareness.
- They have a condition or disability (including a learning disability or cognitive impairment) that means they cannot SMBG by capillary blood glucose monitoring but could use an isCGM device (or have it scanned for them).
- They would otherwise be advised to self-measure at least eight times a day.

Real time CGM (rtCGM) is recommended as an alternative to isCGM only if it is available for the same or lower cost.[6]

Drug treatments

NICE recommends that the choice of drug treatments is based on:[6]

- The person’s individual clinical circumstances, for example comorbidities, contraindications, weight, and risks from polypharmacy.
- The person’s individual preferences and needs.
- The effectiveness of the drug treatments in terms of metabolic response and cardiovascular and renal protection.
- Safety and tolerability of the drug treatment.
- Monitoring requirements.
- The licensed indications or combinations available.
- Cost (if two drugs in the same class are appropriate, choose the option with the lowest acquisition cost).

First line treatment

NICE have produced a visual summary on first line drug treatment for an overview of the recommendations and additional information to support medicines choice.

For adults with type 2 diabetes and chronic kidney disease, follow recommendations on using SGLT2 inhibitors - see the section on diabetic kidney disease.[6]

When considering first line drug treatment choices the individual's cardiovascular status and risk should be first assessed to determine whether they have chronic heart failure, established atherosclerotic CVD or are at high risk of developing CVD.[6]

- Atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, previous coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.
- High risk of developing CVD is defined as:
  - QRISK2 more than 10% in adults aged 40 and over or
  - An elevated lifetime risk of CVD (defined as the presence of one or more cardiovascular risk factors in someone under 40).
- CVD risk factors: hypertension, dyslipidaemia, smoking, obesity, and family history (in a first-degree relative) of premature CVD.[6]

See table 2 for further information regarding all glucose lowering drugs included in current NICE and SIGN guidance.

If the person has no chronic heart failure, established atherosclerotic CVD or they are currently not at high risk of CVD:

- Offer standard-release metformin as first line drug treatment. Gradually increase the dose over several weeks to reduce the risk of gastrointestinal side effects:[6,7]
  - 500mg with breakfast for at least one week,
  - Then 500mg with breakfast and evening meal for at least one week,
  - Then 500mg with breakfast, lunch, and evening meal thereafter; maximum dose 2g daily (in divided doses).[4]
- If gastrointestinal side effects are problematic with standard-release metformin, consider a trial of modified-release metformin.
- If metformin is contraindicated or not tolerated, consider:
  - A dipeptidyl peptidase 4 (DPP-4) inhibitor ('gliptins') – alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin or
  - Pioglitazone or
  - A sulfonylurea (gliclazide, glipizide, tolbutamide) or
  - A sodium-glucose co-transporter-2 (SGLT2) inhibitor (also known as 'flozins') – canagliflozin, dapaglifozin, empagliflozin, ertugliflozin, for people who meet the criteria in NICE [TA390] or NICE [TA572]

If the person has chronic heart failure or established atherosclerotic CVD:

- First offer standard-release metformin as first line drug treatment. Gradually increase the dose over several weeks to reduce the risk of gastrointestinal side effects:[6,7]
  - 500mg with breakfast for at least one week,
  - Then 500mg with breakfast and evening meal for at least one week,
  - Then 500mg with breakfast, lunch, and evening meal thereafter; maximum dose 2g daily (in divided doses).[4]

- If gastrointestinal side effects with standard-release metformin, consider a trial of modified-release metformin.
- Start a SGLT2 inhibitor with proven cardiovascular benefit (currently canagliflozin, dapagliflozin and empagliflozin), in addition to metformin as soon as metformin tolerability is confirmed.
- If metformin is contraindicated or not tolerated, offer a SGLT2 inhibitor alone which has proven cardiovascular benefit (currently canagliflozin, dapagliflozin and empagliflozin).
- Pioglitazone should not be used in patients with heart failure.[7]

SIGN guidelines also recommend that SGLT2 inhibitors with proven cardiovascular benefit (currently canagliflozin, dapagliflozin and empagliflozin) should be considered in individuals with type 2 diabetes and established CVD.[7]

If the person is at high risk of developing CVD:

- Consider an SGLT2 inhibitor with proven cardiovascular benefit (currently canagliflozin, dapagliflozin and empagliflozin) in addition to metformin, as soon as metformin tolerability is confirmed.
- If metformin is contraindicated or not tolerated, consider an SGLT2 inhibitor alone which has proven cardiovascular benefit (currently canagliflozin, dapagliflozin and empagliflozin).[6]

For any adult with type 2 diabetes at any stage after they have started first line treatment:

- If they have or develop chronic heart failure or established atherosclerotic CVD, offer an SGLT2 inhibitor with proven cardiovascular benefit (currently canagliflozin, dapagliflozin and empagliflozin), in addition to current treatment or replace an existing drug with the SGLT2 inhibitor.
- If they are or become at high risk of developing CVD, consider adding an SGLT2 inhibitor with proven cardiovascular benefit (currently canagliflozin, dapagliflozin and empagliflozin) to current treatment or replacing an existing drug with the SGLT2 inhibitor.
- Take into account the person's current treatment regimen and preferences and make a shared decision about switching treatments or adding an SGLT2 inhibitor, as appropriate.[6]

Information on repaglinide has been removed from the NICE guideline.[6] Repaglinide has a limited role in treatment because it is only licensed for monotherapy or in combination with metformin. For people started on repaglinide due to intolerance or contra-indication to metformin and subsequently requiring treatment intensification, would require a complete change in their drug treatment regimen.[15]

Chronic kidney disease (CKD)

For adults with CKD and type 2 diabetes, blood pressure should be reduced to the lowest achievable level to slow the rate of decline of glomerular filtration rate and reduce proteinuria. When proteinuria and hypertension are present the standardised mortality ratio is increased fivefold in men and eightfold in women with type 2 diabetes.[8]

Offer an angiotensin receptor blocker (ARB) or an angiotensin-converting enzyme (ACE) inhibitor (titrated to the highest licensed dose that the person can tolerate) if albumin-to-creatinine ratio (ACR) is 3mg/mmol or more.[6,8]

Offer an SGLT2 inhibitor to adults with diabetes who are taking an ARB or an ACE inhibitor (titrated to the highest licensed dose that the person can tolerate) if their ACR is over 30mg/mmol and they meet the criteria in the marketing authorisation (including relevant eGFR thresholds). Consider an SGLT2 inhibitor (in addition to the ARB or ACE inhibitor) if ACR is between 3 and 30mg/mmol and they meet the criteria in the marketing authorisation (including relevant eGFR thresholds).[6] Dapagliflozin 10mg daily is the only SGLT2 inhibitor with a specific licensed indication for chronic kidney disease - NICE [TA775].[15] The other SGLT2 inhibitors include dosing recommendations for patients with renal impairment.[4,15]

Further treatment options[6]

NICE have produced a visual summary on treatment options if further interventions are needed with an overview of the recommendations and additional information to support medicines choice.

If monotherapy has not continued to control HbA1c to below the person's individually agreed threshold, switch or add treatments from different drug classes up to triple therapy (dual therapy if metformin is contraindicated). Consider adding:[6]

- A DPP-4 inhibitor or
- Pioglitazone or
- A sulfonylurea (SU) or
- An SGLT2 inhibitor for people who meet the criteria in NICE [TA315], NICE [TA572], NICE [TA288], NICE [TA336].

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

- Triple therapy by adding a DPP-4 inhibitor, pioglitazone or a SU or an SGLT2 inhibitor for people who meet the criteria in NICE [TA315], NICE [TA418], NICE [TA336] NICE [TA583] or
- Insulin-based therapy (with or without other drugs). Continue to offer metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies.

If metformin is contraindicated or not tolerated and dual therapy with 2 oral drugs has not continued to control HbA1c, consider insulin (with or without other drugs).

If a person is on triple therapy with metformin and two other oral drugs and one of those is not effective, not tolerated or contraindicated, consider switching that drug for a glucagon-like peptide-1 (GLP-1) agonists to continue triple therapy for adults with type 2 diabetes who:

- Have a body mass index (BMI) of 35kg/m^2 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/m^2 and:
  - For whom insulin therapy would have significant occupational implications or
  - Weight loss would benefit other significant obesity-related comorbidities.[6]

Only offer combination therapy with a GLP-1 agonist and insulin along with specialist care advice, initiation, stabilisation, monitoring and ongoing support from a consultant-led multidisciplinary team.[6]

GLP-1 agonist therapy should only be continued if the person has had a beneficial metabolic response (defined as a reduction of at least 11mmol/mol [1.0%] in HbA1c and weight loss of at least 3% of initial body weight in six months).[6] If beneficial metabolic response is not achieved assess the person's adherence and injection technique.

If the GLP-1 receptor agonist is to be stopped then consider what alternative oral options are available. NICE recommends GLP-1 receptor agonists as an alternative in triple therapy if metformin and two other oral drugs are not effective.[6]

When reviewing or considering changing treatments for adults with type 2 diabetes, think about and discuss the following with the person:

- How to optimise their current treatment regimen before thinking about changing treatments, taking into account factors such as:
  - Adverse effects
  - Adherence to existing medicines
  - The need to revisit advice about diet and lifestyle

  - » Prescribed doses and formulations.
- Stopping medicines that have had no impact on glycaemic control or weight, unless there is an additional clinical benefit, such as cardiovascular or renal protection, from continued treatment (i.e. SGLT2s).
- Whether switching rather than adding drugs could be effective.
- Any initial considerations or rationale for choosing a particular drug treatment.[6]

Starting Neutral Protamine Hagedorn (NPH) insulin instead of an oral medication may need to be considered as an alternative.[6]

Table 2: Properties of glucose lowering agents included in NICE and SIGN guidelines (Refer to the current BNF and individual Summary of Product Characteristics (SPCs) for further details and up to date information regarding interactions)[4,7,15-17]

Class	Drug action	Advantages	Disadvantages	Cost per 28 days (see cost section for cost comparison charts)
Biguanide • Metformin	• ↓ Hepatic glucose production (gluconeogenesis). • ↑ peripheral utilisation of glucose. Note – it is only effective in the presence of insulin, there either needs to be residual functioning pancreatic islet cells or the patient is on injectable insulin therapy.	• 60+ years' experience. • No hypoglycaemia as monotherapy. • Weight loss or stabilisation. • Improved insulin sensitivity. • Can be used in pregnancy.	• Gastro-intestinal side effects – consider gradual dose titration or a trial of MR metformin. • Taste disturbance. • Lactic acidosis (very rare)- see safety section for further information. Monitor for unexplained abdominal pain, nausea and vomiting, anorexia, hypothermia, lethargy, respiratory distress. • Do not prescribe if eGFR is <30ml/min/1.73m^2. • If eGFR is <45ml/min/1.73m^2 - review dose. • Caution in elderly patients. • Reduced vitamin B12 absorption during long term use, at higher doses and in patients with risk factors for vitamin B12 deficiency - monitor serum levels if patients has risk factors or if deficiency is suspected – new onset neuropathy or megaloblastic anaemia. See NICE CKS guidance.	• Metformin 500mg tablets - £3.16 • Metformin 1g tablets - £121.70 • Metformin MR 500mg tablets - £3.16 • Metformin MR 1g tablets - £2.23

Class	Drug action	Advantages	Disadvantages	Cost per 28 days (see cost section for cost comparison charts)
Sodium glucose co-transporter 2 (SGLT2) inhibitors also known as - SGLT2i or "flozins" • Canagliflozin • Dapagliflozin • Empagliflozin • Ertugliflozin	• ↓ renal glucose reabsorption. • ↑ urinary glucose excretion.	• Low risk hypoglycaemia. • ↓ weight. • ↓ renal glucose re-absorption so increase glucose excretion equivalent to a net loss of 200–300 kcal/day. • ↓ Blood pressure. • Dapagliflozin no dose adjustment in renal impairment. (Not Recommended below eGFR<15ml/min/1.73m^2. See individual SPCs for specific recommendations in relation to other SGLT2s). • Beneficial in CVD and CKD. • Dapagliflozin is also licensed for symptomatic chronic heart failure with reduced ejection fraction, CKD. • Empagliflozin also licensed for symptomatic chronic heart failure.	• Risk of diabetic ketoacidosis including life threatening cases - test for ketones. See safety section for further information. • Monitor blood ketones during treatment interruption for surgical procedures or acute serious illness. • Fournier's gangrene (necrotizing fasciitis of the genitalia or perineum). • Increased risk of lower-limb amputation (mainly toes). • Avoid with volume depletion, loop diuretics, polyuria. • Genito-urinary infections are common. • Caution in elderly patients • Glycaemic control of SGLT2 inhibitors is dependent on renal function and reduced in moderate impairment and absent in severe. • Dose of concomitant insulin or drugs which stimulate insulin secretion may need to be reduced – due to risk of hypoglycaemia. • Patients should be advised not to start a low carbohydrate or ketogenic diet without consulting a health professional.	• Ertugliflozin 5mg & 15mg both cost £29.40 • All other SGLT2i in all strengths £36.59

Class	Drug action	Advantages	Disadvantages	Cost per 28 days (see cost section for cost comparison charts)
Dipeptidylpeptidase-4 inhibitor - DPP-4 inhibitor or "Gliptins" • Alogliptin • Linagliptin • Saxagliptin • Sitagliptin • Vildagliptin	• ↑ insulin secretion. • ↓ glucagon secretion.	• Generally well tolerated. • Less risk of hypoglycaemia than sulfonylureas • Weight neutral. • Linagliptin - no dose adjustment needed in renal impairment. Dose adjustment required for other DPP-4 inhibitors	• Acute pancreatitis • Gastrointestinal side effects • ↑ risk of infection with saxagliptin, alogliptin and vildagliptin • Risk of heart failure in patients with existing heart or kidney disease	• Alogliptin all strengths - £26.60 • Linagliptin - £33.26 • Saxagliptin all strengths - £31.60 • Sitagliptin all strengths - £33.26 • Vildagliptin - £33.35
Thiazolidinedione • Pioglitazone	• ↓ peripheral insulin resistance. • ↑ insulin sensitivity.	• Low to no risk of hypoglycaemia as monotherapy. • ↑HDL. • ↓Triglycerides.	• ↑ risk of heart failure – monitor for signs of heart failure: oedema, weight gain. • ↑ risk of bladder cancer – see CKS topic urological cancers. • Patients should be advised to report promptly any haematuria, dysuria, or urinary urgency during treatment. • ↑ risk of bone fractures. • ↑ risk of infection. • Weight gain. • Liver toxicity – monitor liver function • Visual impairment. • Contraindicated in ketoacidosis.	• 15mg tablets - £1.34 • 30mg tablets - £1.88 • 45mg tablets - £2.35

Class	Drug action	Advantages	Disadvantages	Cost per 28 days (see cost section for cost comparison charts)
Sulfonylureas(SU) • Gliclazide • Glimepiride • Glipizide • Tolbutamide	• ↑ endogenous insulin secretion.	• Extensive experience • Can be used as rescue therapy for symptomatic hyperglycaemia.	• Contraindicated in ketoacidosis • Risk of hypoglycaemia – avoid long acting sulfonylureas; glibenclamide, chlorpropamide, glimepiride, particularly in elderly. Glicazide, glipizide and tolbutamide are preferred. • Ensure compliance with DVLA guidance for sulfonylureas. • Only effective if residual pancreatic beta-cell activity is present • Weight gain • Avoid use in pregnancy – risk of neonatal hypoglycaemia.	• Gliclazide 80mg tablets - £1.04 • Glimepiride 4mg tablets - £0.98 • Glipizide 5mg tablets - £1.26 • Glimepiride 2mg tablets - £1.68 • Gliclazide 40mg tablets - £2.32 • Gliclazide 30mg MR tablets - £2.81 • Gliclazide 160mg tablets - £3.27 • Gliclazide 60mg MR tablets - £5.62 • Tolbutamide 500mg tablets – (1tds) - £362.16

Class	Drug action	Advantages	Disadvantages	Cost per 28 days (see cost section for cost comparison charts)
Glucagon-like peptide-1 receptor agonists – (GLP-1 receptor agonists): • Dulaglutide • Exenatide • Liraglutide (Victoza®) • Lixisenatide • Semaglutide • Tirzepatide -licensed 2022. NICE TA expected April 2023.	• ↑ Insulin secretion. • ↓ Glucagon secretion • Slows gastric emptying. • ↑ satiety. • ↓ appetite.	• Low risk hypoglycaemia when used as monotherapy. • ↓ Weight. • Semaglutide is available as a once daily oral tablet as well as injectable. Effect of switching between products is not easily predicted.	• Gastrointestinal side effects. • Acute pancreatitis. • Ketoacidosis with insulin. • Most are subcutaneous Injections only – training required. • Caution in elderly. • Retinopathy- use semaglutide with caution. • Effective contraception needed in women of child bearing potential. • Caution in severe hepatic impairment -semaglutide, liraglutide.	• Dulaglutide all strengths - £73.25 • Exenatide 5 micrograms/0.02ml & 10 micrograms/0.04ml - £76.43 • Exenatide 2mg & 2mg/0.85ml prolonged-release - £73.36 • Liraglutide (Victoza®)- £73.25 • Lixisenatide 10 micrograms/0.2ml - £63.34 • Lixisenatide 20 micrograms/0.2ml - £57.93 • Semaglutide all strengths tablets and injectables - £73.25

Insulin therapy[6]

When starting insulin therapy provide a structured programme using active insulin dose titration that encompasses:

- Injection technique.
- Continuing telephone support.
- Self-monitoring.
- Dose titration to target levels.
- Dietary advice.
- DVLA guidance.
- Managing hypoglycaemia.
- Managing acute changes in plasma glucose control.
- Support from an appropriately trained and experienced healthcare professional.

When insulin is initiated, metformin should be continued with insulin for people without contraindications or intolerances. The continued need for other blood glucose lowering agents should be reviewed. Start insulin therapy with either:

- NPH insulin injected once or twice daily according to need.
- NPH and short-acting insulin (particularly if HbA1c is ≥75mmol/mol [9.0%]), administered separately or as a pre-mixed (biphasic) human insulin preparation.

Consider insulin detemir or insulin glargine as an alternative to NPH if specific administration or lifestyle criteria are met.[6]

When starting an insulin for which a biosimilar is available, use the product with the lowest acquisition cost. If people are already prescribed an insulin for which a lower cost biosimilar is available, discuss the possibility of switching to the biosimilar. This should be a shared decision with the person after discussing their preferences.[6]

Ensure the Medicines and Healthcare products Regulatory Agency (MHRA) guidance on minimising the risk of medication error with high strength, fixed combination and biosimilar insulin products is followed. This includes advice for healthcare professionals.[6]

Intensifying therapy by prescribing insulin 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 further non-insulin treatments options outlined in the NICE pathway.

A summary of treatment is described in algorithm 1. Attachment 1 provides a locally adaptable version of algorithm 1 where local agreed formulary choices can be added.

The PrescQIPP diabetes webkit brings together all the PrescQIPP diabetes resources, data and showcases good practice examples of projects focusing on medicines optimisation in diabetes. Each set of resources contains tools that can be adapted for local use before implementation.

Algorithm 1: Treatment algorithm for type 2 diabetes in adults

- Offer structured education, lifestyle measures, e.g. diet, weight loss, exercise, smoking cessation.
- NICE [NG28] recommends if two drugs in the same class are appropriate, choose the option with the lowest acquisition cost.
- Blood glucose monitoring – do not routinely offer. Only offer in line with DVLA requirements, insulin, sulphonylureas, pregnancy, planning pregnancy or evidence of hypoglycaemic episodes.

Assess HbA1c, CVD risk and kidney function

DPP-4 inhibitor – Dipeptidyl peptidase-4 inhibitor
GLP-1 - Glucagon like peptide-1 receptor agonist
SGLT2i – Sodium glucose cotransporter-2 inhibitor
SU – Sulfonylurea
CI – Contraindication
NPH - neutral protamine Hagedorn insulin
GI - Gastrointestinal

Not at high CVD risk, offer:

- Metformin standard-release - Gradually increase dose over several weeks to minimise the risk of GI disturbance.
- Metformin MR if GI disturbance intolerable.
- If metformin is contraindicated, consider:
  - DPP-4 inhibitor or
  - Pioglitazone or
  - SU
  - SGLT2i for some people (canagliflozin, dapagliflozin, empagliflozin,ertugliflozin).

Chronic heart failure or established atherosclerotic CVD consider:

- Metformin standard-release - Gradually increase dose over several weeks to minimise the risk of GI disturbance.
- Metformin MR if GI disturbance intolerable.
- As soon as metformin tolerability is confirmed offer a SGLT2i with proven CV benefit (canagliflozin, dapagliflozin and empagliflozin).
- If metformin is contraindicated offer a SGLT2i.

High risk of CVD offer:

- Metformin standard-release - Gradually increase dose over several weeks to minimise the risk of GI disturbance.
- Metformin MR if GI disturbance intolerable.
- As soon as metformin tolerability is confirmed consider a SGLT2i with proven CV benefit (canagliflozin, dapagliflozin and empagliflozin).
- If metformin is contraindicated, consider a SGLT2i.

At any stage after first line treatment:

- If they have or develop chronic heart failure or established atherosclerotic CVD offer a SGLT2i with proven CV benefit (canagliflozin, dapagliflozin and empagliflozin - if not already prescribed).
- If they become or develop high risk CVD consider a SGLT2i with proven CV benefit (canagliflozin, dapagliflozin and empagliflozin - if not already prescribed).

Treatment options if further interventions are needed: HbA1c not controlled below individually agreed threshold

If monotherapy has not reduced HbA1c below individually agreed target, consider adding:

- A DPP-4 inhibitor or
- Pioglitazone or
- SU or
- An SGLT2i for some people.

If dual therapy (metformin and another oral drug) has not reduced HbA1c below agreed target, consider:

- Triple therapy by adding a DPP-4 inhibitor or pioglitazone or SU or an SGLT2i for some people.
- Insulin.
- If metformin is CI/not tolerated and dual therapy with two oral drugs has not controlled HbA1c consider insulin

- If triple therapy (metformin and two other oral drugs) is not effective, not tolerated or CI, consider triple therapy by switching one drug for a GLP-1 if:
- BMI ≥35kg/m^2 (Adjust accordingly for high risk individuals, ethnic minorities, co-morbidities associated with obesity etc.)
- BMI <35kg/m^2 if insulin would have significant occupational implications or weight loss would beneficial.

Initiating insulin: Continue metformin if not CI/not tolerated. Review the continued need for other blood glucose lowering therapies. When starting an insulin for which a biosimilar is available, use the product with the lowest acquisition cost.

Offer NPH insulin once or twice daily.

Consider starting both NPH and short acting insulin.

- Separately or
- Pre-mixed - biphasic

Consider insulin detemir or glargine as an alternative to NPH for some people.

Treatment of hypoglycaemia

Hypoglycaemia is a lower than normal blood glucose concentration and is generally defined as blood glucose levels less than 3.5mmol/L.[4,15,18] It is the most common side effect of insulin and sulfonylureas in the treatment of all types of diabetes mellitus and presents a major barrier to satisfactory long-term glycaemic control. Metformin, pioglitazone, DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists are associated with a low risk of hypoglycaemia as monotherapy. Where prescribed without insulin or sulfonylurea therapy, these antidiabetic agents are unlikely to result in hypoglycaemia.[15]

Symptoms

Early signs of a low blood sugar level include:[18]

- Sweating
- Feeling tired
- Dizziness
- Feeling hungry
- Tingling lips
- Feeling shaky or trembling
- A fast or pounding heartbeat (palpitations)
- Becoming easily irritated, tearful, anxious or moody
- Turning pale.

If a low blood sugar level is not treated, you may get other symptoms, such as:

- Weakness
- Blurred vision
- Confusion or difficulty concentrating
- Unusual behaviour, slurred speech or clumsiness (like being drunk)
- Feeling sleepy
- Seizures or fits
- Collapsing or passing out.

A “hypo” can also occur whilst sleeping and may cause the patient to wake up during the night. Headaches, tiredness or damp sheets from sweat may also be evident the following morning.[18]

Treatment

Advise people with type 2 diabetes if their blood sugar level is less than 3.5mmol/L or if they have hypoglycaemic symptoms to have 15-20g of glucose. A sugary drink or snack like a small glass of non-diet variety fizzy drink, 150–200ml of pure fruit juice, 4 to 5 jelly babies or three to six glucose tablets should provide this amount.[15,18] They should retest their blood sugar after ten minutes. If it has improved and they feel better, they should eat a slow-release carbohydrate. This could be part of a main meal if it is time to eat it or, if not, a snack such as a slice of bread or toast, a couple of biscuits, or a glass of cows’ milk. If there is no improvement or no change 10 to 15 minutes after a sugary drink or snack, they should have another and repeat the reading 10 to 15 minutes after that and eat a slow-release carbohydrate.[15,18]

Self care treatment of hypoglycaemia is usually appropriate for the majority of people, if the person is conscious, but uncooperative they will need to be treated with glucose 40% oral gel via buccal administration. This should be given as 1.5-2 tubes of glucose 40% oral gel, repeated after 15 minutes

if necessary. Glucose 40% oral gels are available to buy over-the-counter and can be prescribed if appropriate. The following brands are currently listed in the BNF:[15]

- Dextrogel 40% gel
- GlucoBoost 40% gel
- GlucoGel 40% gel
- Rapilose 40% gel
- YourGLUCO 40% gel.

In an emergency, if the patient has a decreased level of consciousness caused by hypoglycaemia, put the person in the recovery position and do not put anything in their mouth – so they do not choke. Call 999 for an ambulance, if an injection of glucagon is not available, or it is not known how to use it, or the person had alcohol before their hypoglycaemic episode. If an injection of glucagon is available and a family member or friend has been shown how to use it, give it to them immediately and call 999. If glucagon is not effective after ten minutes, glucose 10% intravenous infusion should be given.[15,18] Glucagon is a prescription only medicine and available as:[15,16]

- GlucaGen Hypokit 1mg.
- Ogluo 1mg.

Reviewing drug treatments[6]

The person's needs and circumstances should be reassessed at each review. Consider stopping any medicines that are not effective, have no impact on glycaemic control or weight, unless there is an additional clinical benefit, such as cardiovascular or renal protection, from continued treatment.

When reviewing treatments or considering changing treatments think and discuss how to optimise the current treatment regimen. Consider adverse effects, adherence, revisiting diet advice, lifestyle advice, prescribed doses and formulations. Attachments 6-10 audits can be used.

Managing cardiovascular risk

In the 2022 update to NG28, NICE considered which pharmacological therapies are most effective at providing cardiovascular and other benefits in addition to blood glucose control in people with type 2 diabetes.[6] Since the publication of the guideline in 2015 new glucose lowering drugs SGLT2 inhibitors, DPP-4 inhibitors and GLP-1 agonists have been licensed. These cardiovascular outcome trials (CVOTs) are different in design to trials that compare treatments to each other where everyone in a particular arm is on the same treatment and therefore cannot be combined with these trials directly for analysis. However, the results of these different formats of trials can be combined in an economic model to enable an assessment of the effectiveness and cost-effectiveness of the drugs taking the newly identified cardiovascular benefits into account.[19] Evidence from clinical trials looking at cardiovascular benefits, network meta-analyses, and economic modelling, showed that some treatments were effective at improving cardiovascular outcomes and were likely to be cost effective. All of these trials recruited people with established CVD, and some also included people with a high risk of developing CVD. For people without high cardiovascular risk, the NICE guideline review committee agreed there was more uncertainty over whether the same level of cardiovascular benefits is seen.[6,19]

Choosing an SGLT2 inhibitor with cardiovascular benefit

The evidence reviewed by the committee showed that SGLT2 inhibitors as a class of drugs were most likely to be cost effective in combination with metformin, although the incremental cost-effectiveness ratio (ICER) varied between different drugs in the class and in different scenarios in the model. The exception to this was dapagliflozin, which was cost effective at a threshold of £20,000 per quality-adjusted life year in the base-case analysis and across a range of model scenarios. However, the

committee agreed there was too much uncertainty in the clinical data, and therefore the economic modelling, for them to be confident that these different ICERs represented true underlying differences in cost effectiveness between the SGLT2 inhibitors. There were also varying levels of certainty in the clinical trials and the network meta-analyses about:[6]

- Which individual SGLT2 inhibitors were effective at improving cardiovascular outcomes.
- Whether there were real differences in cardiovascular benefits between the different SGLT2 inhibitors.

Taking the cost effectiveness and clinical results into account, the committee decided against recommending only dapagliflozin and instead made recommendations for the SGLT2 inhibitors as a class. They recognised that there was greater uncertainty around the cardiovascular benefits associated with ertugliflozin than there was for empagliflozin, canagliflozin and dapagliflozin. This was because ertugliflozin did not consistently show a reduction in heart failure compared with placebo in the network meta-analyses (it depended on the model used), and it was not statistically significantly better than placebo for the 3-point major adverse cardiovascular events (MACE) outcome. The committee therefore decided to refer to 'SGLT2 inhibitors with proven cardiovascular benefit' in the recommendations. This was to enable prescribers to select a particular drug from the class of SGLT2 inhibitors that they thought was clinically appropriate for each person, while allowing the recommendation to remain current even if additional evidence or new SGLT2 inhibitors become available.[6,19]

Since the consideration of evidence by the NICE Guideline update committee, the following additional trial information has been published.[20-22]

The EMPEROR-preserved trial assessed the effect of empagliflozin (10mg daily) in 5,988 patients, men and women, aged ≥18 years, with chronic HF (New York Heart Association (NYHA) class II, III or IV) for ≥3 months and an ejection fraction of more than 40%. Nearly half of the patients had type 2 diabetes (48.9% in the empagliflozin-treated group and 49.2% in the placebo group). The primary endpoint was CV death or hospitalisation for heart failure (HHF). The secondary outcomes were the occurrence of all adjudicated HHF, including first and recurrent events and the rate of decline in the eGFR during double-blind treatment.[20,21]

Over a median of 26.2 months or 2.2 years, empagliflozin showed a significant improvement of the primary outcomes, with an event occurring in 415 of 2,997 patients (13.8%) in the empagliflozin group and in 511 of 2,991 patients (17.1%) in the placebo group (hazard ratio (HR), 0.79; 95% confidence interval [CI], 0.69 to 0.90; p<0.001). This effect was mainly related to a lower risk of HHF, [HR 0.71; [95% CI 0.60 to 0.83]), in the empagliflozin group and a slight decrease in CV death risk (HR 0.91 [95% CI 0.76 to 1.09]). The effects of empagliflozin appeared consistent in patients with (HR 0.79 [95% CI 0.67 to 0.94]) or without diabetes (HR 0.78 [95% CI 0.69 to 0.90]). The total number of HHF was lower in the empagliflozin group than in the placebo group (407 with empagliflozin and 541 with placebo; HR 0.73; 95% CI, 0.61 to 0.88; p<0.001). The decline rate in the eGFR was slower in the empagliflozin-treated group compared to placebo (−1.25 vs. −2.62mL/min/1.73m^2 per year; Between-group difference in slope: 1.36mL/min/1.73m^2 per year [95% CI 1.06 to 1.66]; p < 0.001). Uncomplicated genital and urinary tract infections and hypotension were reported more frequently with empagliflozin.[20,21]

The DELIVER trial randomly assigned 6,263 patients with heart failure and a left ventricular ejection fraction of more than 40% to receive either dapagliflozin (at a dose of 10mg once daily) or matching placebo, in addition to usual therapy. The primary outcome was a composite of worsening heart failure (which was defined as either an unplanned hospitalisation for heart failure or an urgent visit for heart failure) or cardiovascular death. Over a median of 2.3 years, the primary outcome occurred in 512 of 3,131 patients (16.4%) in the dapagliflozin group and in 610 of 3,132 patients (19.5%) in the placebo group (HR 0.82; 95% CI, 0.73 to 0.92; p<0.001). Worsening heart failure occurred in 368 patients (11.8%) in the dapagliflozin group and in 455 patients (14.5%) in the placebo group (HR

0.79; 95% CI, 0.69 to 0.91). Cardiovascular death occurred in 231 patients (7.4%) and 261 patients (8.3%), respectively (HR 0.88; 95% CI, 0.74 to 1.05). Total events and symptom burden were lower in the dapagliflozin group than in the placebo group. Results were similar among patients with a left ventricular ejection fraction of 60% or more and those with a left ventricular ejection fraction of less than 60%, and results were similar in prespecified subgroups, including patients with or without diabetes. The incidence of adverse events was similar in the two groups.[22]

Hypertension

Hypertension is positively related to the risk of CVD death, with a progressive increase in risk with rising systolic pressures. Each 10mm Hg reduction in systolic pressure is associated with a 15% (95% CI 12 to 18%) reduction in the risk of CVD death over ten years.[8] The diagnosis, treatment and monitoring of hypertension is broadly the same for people with type 2 diabetes as for other people.[6] NICE guideline [NG136] - Hypertension in adults: diagnosis and management includes information on identifying and treating primary hypertension in people aged 18 and over, including people with type 2 diabetes. It aims to reduce the risk of cardiovascular problems such as heart attacks and strokes by helping healthcare professionals to diagnose hypertension accurately and treat it effectively.[23]

Antiplatelet treatment

Do not offer antiplatelet therapy (aspirin or clopidogrel) to adults with type 2 diabetes without CVD.[6] NICE clinical guidance [CG181] - CVD: risk assessment and reduction, including lipid modification and NICE guideline [NG185] - Acute coronary syndromes include specific recommendations on the primary and secondary prevention of CVD in adults with type 2 diabetes.[24,25]

Managing complications

Chronic kidney disease (CKD)

Refer to chronic kidney disease above.

Eye disease

When adults are diagnosed with type 2 diabetes, refer them immediately to the local eye screening service. Encourage adults to attend eye screening and explain that it will help them to keep their eyes healthy and help to prevent problems with their vision. An emergency review by an ophthalmologist is required if a person has sudden loss of vision, rubeosis iridis, pre-retinal or vitreous haemorrhage or retinal detachment.[6] Tight control of blood glucose reduces the risk of onset and progression of diabetic eye disease in type 2 diabetes. Reducing HbA1c by 16.4mmol/mol (1.5%) and, if possible, to 53mmol/mol (7%) in type 1 and 2 diabetes and reducing blood pressure to 144/82mmHg in type 2 diabetes reduces the incidence and progression of sight-threatening diabetic eye disease.[8]

Diabetic foot problems

Based on United Kingdom population surveys, diabetic foot problems are a common complication of diabetes with prevalence of 23-42% for neuropathy, 9-23% for vascular disease and 5-7% for foot ulceration. Amputation rates are higher in patients with diabetes than patients without diabetes.[8]
All patients with diabetes should be screened to assess their risk of developing a foot ulcer. Patients with active diabetic foot disease should be referred to a multidisciplinary diabetic foot care service.[8]
NICE [NG19] – Diabetic foot problems: prevention and management has guidance on preventing and managing foot problems in children, young people and adults with diabetes.[6]

Erectile dysfunction

Assess, educate, and support men with type 2 diabetes who have problematic erectile dysfunction, addressing contributory factors such as CVD as well as possible treatment options. They should be offered the opportunity to discuss erectile dysfunction as part of their annual review.[6]

Consider a phosphodiesterase-5 inhibitor to treat problematic erectile dysfunction. Initially choose the generic drug with the lowest acquisition cost and take into account any contraindications. After discussion, refer men with type 2 diabetes to a service offering other medical, surgical or psychological management of erectile dysfunction if treatment (including a phosphodiesterase-5 inhibitor, as appropriate) has been unsuccessful.[6]

Peripheral neuropathy

There is good evidence that several agents can improve symptom control and quality of life in painful diabetic peripheral neuropathy, however the evidence base for direct comparison of different agents is limited.[8] Guidance on managing painful diabetic peripheral neuropathy in adults with type 2 diabetes is included in NICE [CG173] - Neuropathic pain in adults: pharmacological management in non-specialist settings.[6]

Autonomic neuropathy

Autonomic neuropathy should be considered for adults who:[6]

- Lose the warning signs of hypoglycaemia – consider the possibility of contributory sympathetic nervous system damage.
- Have unexplained diarrhoea that happens particularly at night – consider the possibility of autonomic neuropathy affecting the gut.
- Have unexplained bladder-emptying problems - investigate the possibility of autonomic neuropathy affecting the bladder.

In managing autonomic neuropathy symptoms, include specific interventions indicated by the manifestations, for example, for abnormal sweating or nocturnal diarrhoea. If an adult with type 2 diabetes and autonomic neuropathy is prescribed tricyclic drugs and antihypertensive drug treatments, be aware of the increased likelihood of side effects such as orthostatic hypotension.[6]

Gastroparesis

Gastroparesis is a long-term condition where the stomach cannot empty in the normal way. It is thought to be the result of a problem with the nerves and muscles that control how the stomach empties. If these nerves are damaged, the muscles of the stomach may not work properly, and the movement of food can slow down. Symptoms of gastroparesis may include:[26]

- Feeling full very quickly when eating.
- Feeling sick (nausea) and vomiting.
- Loss of appetite.
- Weight loss.
- Bloating.
- Abdominal pain or discomfort.
- Heartburn.

Think about a diagnosis of gastroparesis in adults with type 2 diabetes who have erratic blood glucose control or unexplained gastric bloating or vomiting. If gastroparesis is suspected, consider referring adults with type 2 diabetes to specialist services if:[6]

- The differential diagnosis is in doubt.
- The person has persistent or severe vomiting.

To treat vomiting caused by gastroparesis in adults with type 2 diabetes consider alternating the use of erythromycin (off-label use) and metoclopramide. Domperidone should only be considered

in exceptional circumstances, for example if it is the only effective treatment. Domperidone is now restricted to use in the relief of nausea and vomiting only. It should be prescribed at the lowest effective dose for the shortest possible time (treatment duration should not exceed one week) due to the risks of cardiac side effects.[26,27]

Table 3: Summary of the management of complications of type 2 diabetes[6,8,15,26,27]

Complication	Management
CKD	• Offer ARB or ACE inhibitor if ACR is ≥ 3mg/mmol. • Offer a SGLT2 inhibitor if ACR is >30mg/mmol and prescribed an ARB or ACE inhibitor. • Consider a SGLT2 inhibitor if ACR is between 3 and 30mg/mmol and prescribed an ARB or ACE inhibitor. • Dapagliflozin 10mg daily is specifically licenced for CKD. Other SGLT2 inhibitors have dose recommendations for use in patients with renal impairment.
Eye disease	• Refer to the local eye screening service on type 2 diagnosis. • Encourage patients to attend regularly eye screening and explain it will help them to keep their eyes healthy and prevent problems with their vision. • Emergency review by an ophthalmologist is required sudden loss of vision, rubeosis iridis, pre-retinal or vitreous haemorrhage or retinal detachment develop. • Tight control of blood glucose reduces the risk of onset and progression - reducing HbA1c by 16.4mmol/mol (1.5%) and, if possible, to 53mmol/mol (7%) in type 1 and 2 diabetes and blood pressure to 144/82mm Hg reduces the incidence and progression of sight-threatening diabetic eye disease.
Foot problems	• Screen all patients to assess risk of developing a foot ulcer. Diabetic foot problems are a common complication, with a prevalence of 23 - 42% for neuropathy, 9 - 23% for vascular disease and 5 - 7% for foot ulceration. Amputation rates are higher in diabetes patients. • If active foot disease refer to diabetic foot care service. • Patients with limb threatening or life threatening diabetic foot problems, (e.g ulceration with fever or any sign of sepsis, ulceration with limb ischaemia, possible deep seated soft tissue or bone infection, gangrene), should be referred immediately to acute services and the multidisciplinary foot care team informed according to local protocols and pathways. • See NICE guidelines [NG19]
Erectile dysfunction (ED)	• Assess, educate, and support men with type 2 diabetes who have problematic ED. Offer the opportunity to discuss ED as part of their annual review. • Address contributory factors, such as CV disease, as well as possible treatment options. • Consider a phosphodiesterase-5 inhibitor to treat problematic ED – choose the generic drug with the lowest acquisition cost and take into account any contraindications. • If unsuccessful offer referral for other medical, surgical or psychological management

Complication	Management
Peripheral neuropathy	• Good evidence that several agents can improve symptom control and quality of life – evidence base for direct comparison of agents is limited. • See NICE guidelines [CG173] – neuropathic pain in adults
Autonomic neuropathy	• Consider as a possibility in patients who lose warning signs of hypoglycaemia, have unexplained diarrhoea particularly at night or unexplained bladder emptying problems, • Treat the symptoms the patient has e.g. abnormal sweating or nocturnal diarrhoea. • Increased likelihood of side effects, such as orthostatic hypertension with tricyclic drugs and antihypertensives.
Gastroparesis	• Long term condition. Caused by damage to nerves responsible for controlling how the stomach empties, which slows down the passage of food through the gut. Symptoms include: feeling full quickly, nausea and vomiting, loss of appetite, weight loss, bloating, abdominal pain or discomfort, heartburn. • Consider diagnosis of gastroparesis for type 2 diabetes who have erratic blood glucose control with unexplained gastric bloating or vomiting. Consider referral to specialist services if diagnosis in doubt or symptoms are persistent and/or severe. • No strong evidence that any available anti-emetic therapy is effective – some patients report benefit. • Consider alternating the use of erythromycin (off-label use) and metoclopramide. • Domperidone should only be used in exceptional circumstances - restricted to use in the relief of nausea and vomiting. Prescribe at the lowest effective dose for the shortest possible time. Do not exceed one week due to the risks of cardiac side effects.

Safety

Metformin

Renal function

Before starting treatment, check renal function and if eGFR is less than 30ml/min/1.73m^2 then do not start metformin.[4] During treatment renal function should be monitored at least once a year in people with normal renal function and at least twice a year in people with additional risk factors for renal impairment, such as the elderly, or if deterioration in renal function is suspected:[4]

- If eGFR is below 45ml/minute/1.73m^2 the dose of metformin should be reviewed, refer to the SPC.
- If eGFR falls below 30ml/minute/1.73m^2 then metformin should be stopped.

Treatment should be stopped in patients who are at risk of tissue hypoxia or sudden deterioration in renal function.

Lactic Acidosis

This is rare but potentially life-threatening. It has an insidious onset with non-specific signs and symptoms, such as abdominal pain, anorexia, hypothermia, lethargy, nausea, respiratory distress, and vomiting. Stop metformin treatment if eGFR is less than 30ml/min/1.73m^2.[4]

Pregnancy

Following a European review of data from a non-interventional cohort study of population registries in Finland (the CLUE study), the product information for metformin has been updated to permit the use of metformin during pregnancy and the periconceptional phase as an addition or an alternative to insulin, if clinically needed. The Medicines for Women's Health Expert Advisory Group of the Commission on Human Medicines has also reviewed the data from the study and agreed that the product information should be updated.[28]

Vitamin B12 deficiency

Decreased vitamin B12 levels, or vitamin B12 deficiency, is now considered to be a common side effect in people on metformin treatment, especially in those receiving a higher dose or longer treatment duration and in those with existing risk factors. Checking vitamin B12 serum levels in people being treated with metformin who have symptoms suggestive of vitamin B12 deficiency, for example extreme tiredness, a sore and red tongue, pins and needles, or pale or yellow skin. Consider periodically monitoring people with risk factors for vitamin B12 deficiency. Risk factors include:[17]

- Baseline vitamin B12 levels at the lower end of the normal range.
- Conditions associated with reduced vitamin B12 absorption (such as elderly people and those with gastrointestinal disorders such as total or partial gastrectomy, Crohn's disease and other bowel inflammatory disorders, or autoimmune conditions).
- Diets with reduced sources of vitamin B12 (such as strict vegan and some vegetarian diets).
- Concomitant medication known to impair vitamin B12 absorption (including proton pump inhibitors or colchicine).
- Genetic predisposition to vitamin B12 deficiency, such as intrinsic factor receptor deficiency (Imerslund-Gräsbeck syndrome) and transcobalamin II deficiency.

SGLT2 inhibitors

Diabetic ketoacidosis

Before starting an SGLT2 inhibitor, check whether the person may be at increased risk of diabetic ketoacidosis (DKA):[4]

- If they have had a previous episode of DKA.
- If they are unwell with intercurrent illness.
- If they are following a very low carbohydrate or ketogenic diet.

Any modifiable risks for DKA should be addressed before starting an SGLT2 inhibitor, e.g. people who are following a very low carbohydrate or ketogenic diet.[4] People taking SGLT2 inhibitors should be advised to stop treatment immediately and seek medical advice if any clinical features of DKA develop.[4,6] Symptoms of DKA include:[29]

- Urinating more than usual
- Feeling very thirsty
- Being sick
- Stomach pain
- Breath that smells fruity (like pear drop sweets, or nail varnish)
- Deep or fast breathing
- Feeling very tired or sleepy
- Confusion
- Passing out.

Driving

Adult patients with type 2 diabetes at risk of recurrent hypoglycaemia, particularly those on insulin and or sulfonylureas should follow the current DVLA guidance in relation to fitness to drive. Different recommendations have been issued for different classes of anti-diabetic drug. There is also separate recommendations for group one drivers (car and motorcycle) and group two drivers (bus or lorry). The guidance should be checked for the latest information.

Drug Safety Updates

There are a number of Drug Safety Updates relating to the use of SGLT2 inhibitors:

- MHRA/CHM advice (updated April 2016): SGLT2 inhibitors updated advice on the risk of diabetic ketoacidosis - Test for raised ketones in patients with ketoacidosis symptoms, even if plasma glucose levels are near-normal.[30]
- MHRA/CHM advice (March 2020): SGLT2 inhibitors: monitor ketones in blood during treatment interruption for surgical procedures or acute serious medical illness – SGLT2 inhibitor treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses and ketone levels measured, preferably in blood rather than urine. Treatment may be restarted when the ketone values are normal and the patient's condition has stabilised.[31]
- MHRA/CHM advice (February 2019): SGLT2 inhibitors: reports of Fournier's gangrene (necrotising fasciitis of the genitalia or perineum) - If Fournier's gangrene is suspected, stop the SGLT2 inhibitor and start treatment urgently (including antibiotics and surgical debridement). Fournier's gangrene is a rare but potentially life-threatening infection that requires urgent medical attention.[32]
- MHRA/CHM advice (updated March 2017): Increased risk of lower-limb amputation (mainly toes) - Canagliflozin may increase the risk of lower-limb amputation (mainly toes) in patients with type 2 diabetes. Evidence does not show an increased risk for dapagliflozin and empagliflozin, but the risk may be a class effect. Preventive foot care is important for all patients with diabetes.[33]

The manufacturer advises that the dose of concomitant insulin or drugs that stimulate insulin secretion may need to be reduced when given with an SGLT2 inhibitor due to the risk of hypoglcaemia.[15]

DPP-4 inhibitors

Liver and kidney function should be checked before starting treatment with saxagliptin, vildagliptin, and alogliptin. In people with renal impairment doses should be reduced to:[4,15]

- Alogliptin 12.5mg once daily if eGFR is 30–50ml/minute/1.73m^2. Reduce to 6.25mg once daily if eGFR is less than 30ml/minute/1.73m^2.
- Saxagliptin 2.5mg once daily in moderate to severe renal impairment. Avoid in end-stage renal disease requiring haemodialysis.[15]
- Sitagliptin 50mg once daily if eGFR is 30–45ml/minute/1.73m^2. Reduce to 25mg once daily if eGFR is less than 30ml/minute/1.73m^2.
- Vildagliptin 50mg once daily if eGFR is less than 50ml/minute/1.73m^2.

The exception is linagliptin where no dose adjustment is required.[4]

Avoid vildagliptin in hepatic impairment and avoid saxagliptin and alogliptin if severe hepatic impairment.[4]

Avoid vildagliptin in severe heart failure and avoid alogliptin if moderate to severe heart failure.[4]

Pioglitazone

As pioglitazone is associated with several long term risks its ongoing benefit to the patient should be reviewed three to six months after treatment is initiated, and regularly thereafter. Stop pioglitazone in people who do not respond adequately to treatment (i.e. no adequate change in HbA1c).[4,15,35]

Liver function

Before starting treatment with pioglitazone monitor liver function tests (LFTs). If alanine aminotransferase (ALT) is more than 2.5 times the upper limit of normal (ULN), or there is any other evidence of liver disease, do not start treatment. Monitor LFTs periodically, based on clinical judgement.[4]

Heart failure

Pioglitazone should not be used in patients with heart failure or a history of heart failure.

Assess the risk of heart failure and bone fracture.[4] MHRA/CHM advice (December 2014): Insulin combined with pioglitazone: risk of cardiac failure.

Monitor for signs and symptoms of heart failure, such as weight gain or oedema, during treatment. Stop pioglitazone if any deterioration in cardiac function is seen. This is particularly important where pioglitazone is used in combination with insulin.[4,15,34,35]

Bladder cancer

Before starting pioglitazone assess the risk of bladder cancer. Risk factors include increasing age, current or past history of smoking, exposure to some occupational or chemotherapy drugs, such as cyclophosphamide and previous radiation therapy to the pelvic region. MHRA/CHM advice (December 2014): Pioglitazone: risk of bladder cancer. Use of pioglitazone is associated with a small increased risk of bladder cancer. Observational studies report relative risks ranging 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. The increase in absolute risk is therefore likely to be small. Healthcare professionals should be aware of new warnings and precautions for use in at-risk patients, such as patients with active bladder cancer or with a history of bladder cancer, and those with uninvestigated haematuria, should not receive pioglitazone.[35]

Sulfonylureas

Hypoglycaemia and driving

The sulfonylureas (glibenclamide, gliclazide, glimepiride, glipizide, tolbutamide) may cause hypoglycaemia. The risk of hypoglycaemia should be discussed with the patient, especially when concomitant glucose-lowering drugs are prescribed. Drivers need to be particularly careful to avoid hypoglycaemia and should be warned of the problems.[15] Ensure compliance with DVLA guidance. Hypoglycaemia is more likely with long-acting sulfonylureas such as glimepiride or glibenclamide, which have been associated with severe, prolonged and sometimes fatal cases of hypoglycaemia.

Licensed glibenclamide tablets are not available.[15] The BNF for children has guidelines for treatment of neonates and children.

Sulfonylureas are also associated with modest weight gain, probably due to increased plasma-insulin concentrations.[15]

Rescue therapy

Sulfonylureas or insulin can be used as rescue therapy at any phase of treatment to reduce high blood sugars if an adult with type 2 diabetes is symptomatically hyperglycaemic. Review treatment when blood glucose control has been achieved.[6]

GLP-1 agonists

The GLP-1 receptor agonists, dulaglutide, exenatide, liraglutide and lixisenatide, should be reserved for combination therapy when other treatment options have failed.

MHRA/CHM advice (June 2019): GLP-1 receptor agonists: reports of diabetic ketoacidosis when concomitant insulin was rapidly reduced or discontinued. Serious and life-threatening cases of diabetic

ketoacidosis have been reported in patients with type 2 diabetes mellitus on a combination of a GLP-1 receptor agonist and insulin, particularly after discontinuation or rapid dose reduction of concomitant insulin. Healthcare professionals are advised that any dose reduction of insulin should be done in a stepwise manner with careful blood glucose self-monitoring, particularly when GLP-1 receptor agonist therapy is initiated. Patients should be informed of the risk factors for and signs and symptoms of diabetic ketoacidosis and advised to seek immediate medical attention if these develop.[15]

Only offer combination therapy with a GLP-1 receptor agonist and insulin along with specialist care advice and ongoing support from a consultant-led multidisciplinary team.[6]

Costs and savings

All data referred to are from NHSBSA Aug-Oct 22 or Public Health Scotland Aug-Oct 22.

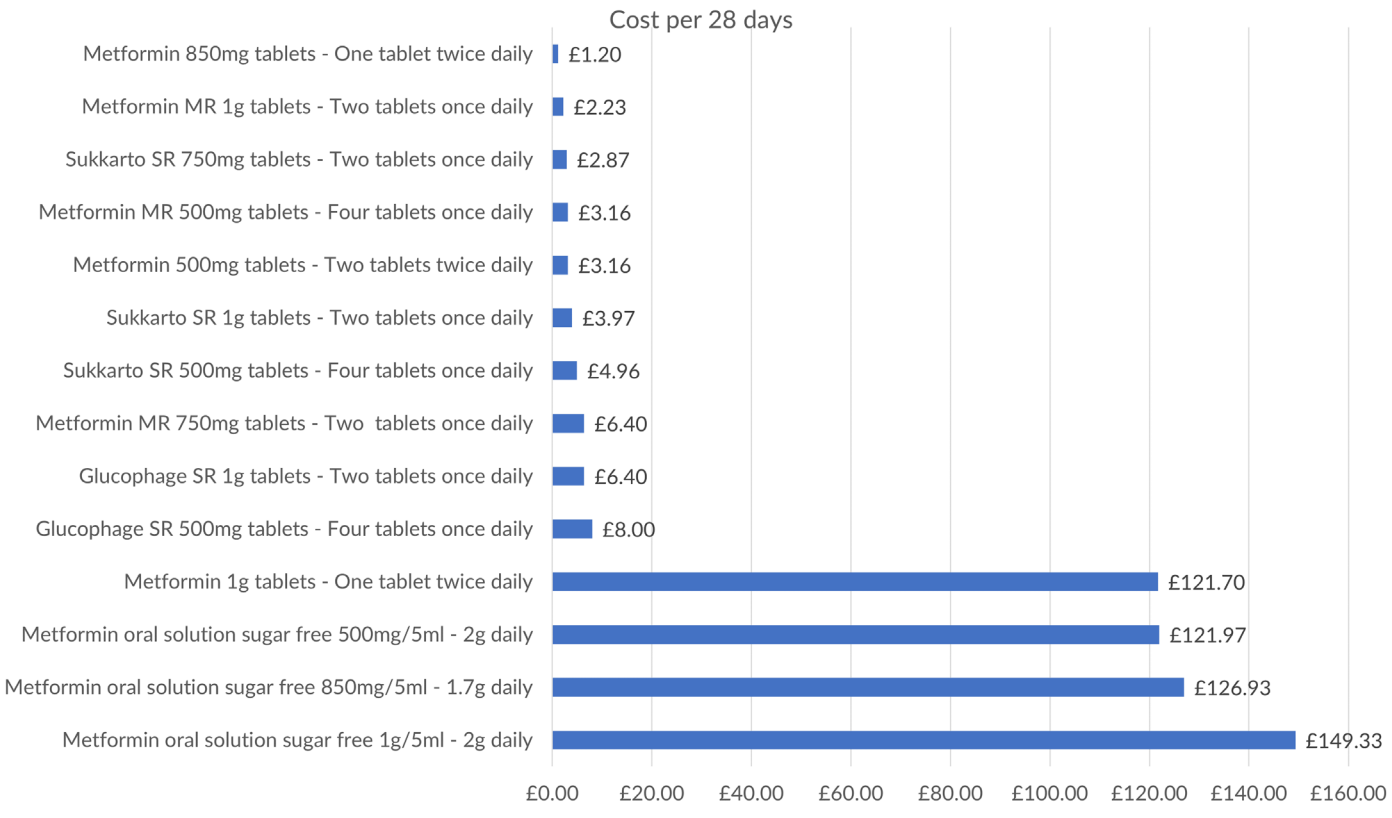
Antidiabetic drugs were the most prescribed treatment for diabetes in England with 43.1 million items prescribed in 2020/21 at a cost of £686 million. The costs of antidiabetic drugs have increased by 62% since 2015/16 from £423 million.[5] Currently, in England, Wales and Scotland, £922 million is spent annually on prescribing of antidiabetic drugs.

The focus is to improve outcomes through medication review. Any changes to medication should consider patient safety and outcomes. Any switches should be undertaken on an individual basis considering all necessary factors for the individual patient. There are significant differences in costs between metformin or sulfonylureas and the newer oral hypoglycaemics.

Metformin

Up-titrate metformin as appropriate (unless not tolerated or contra-indicated) prior to addition of other agents. If gastrointestinal side effects are experienced with the standard-release metformin consider a trial of modified-release metformin.[6,16]

Chart 1: Metformin cost comparisons[15,16]



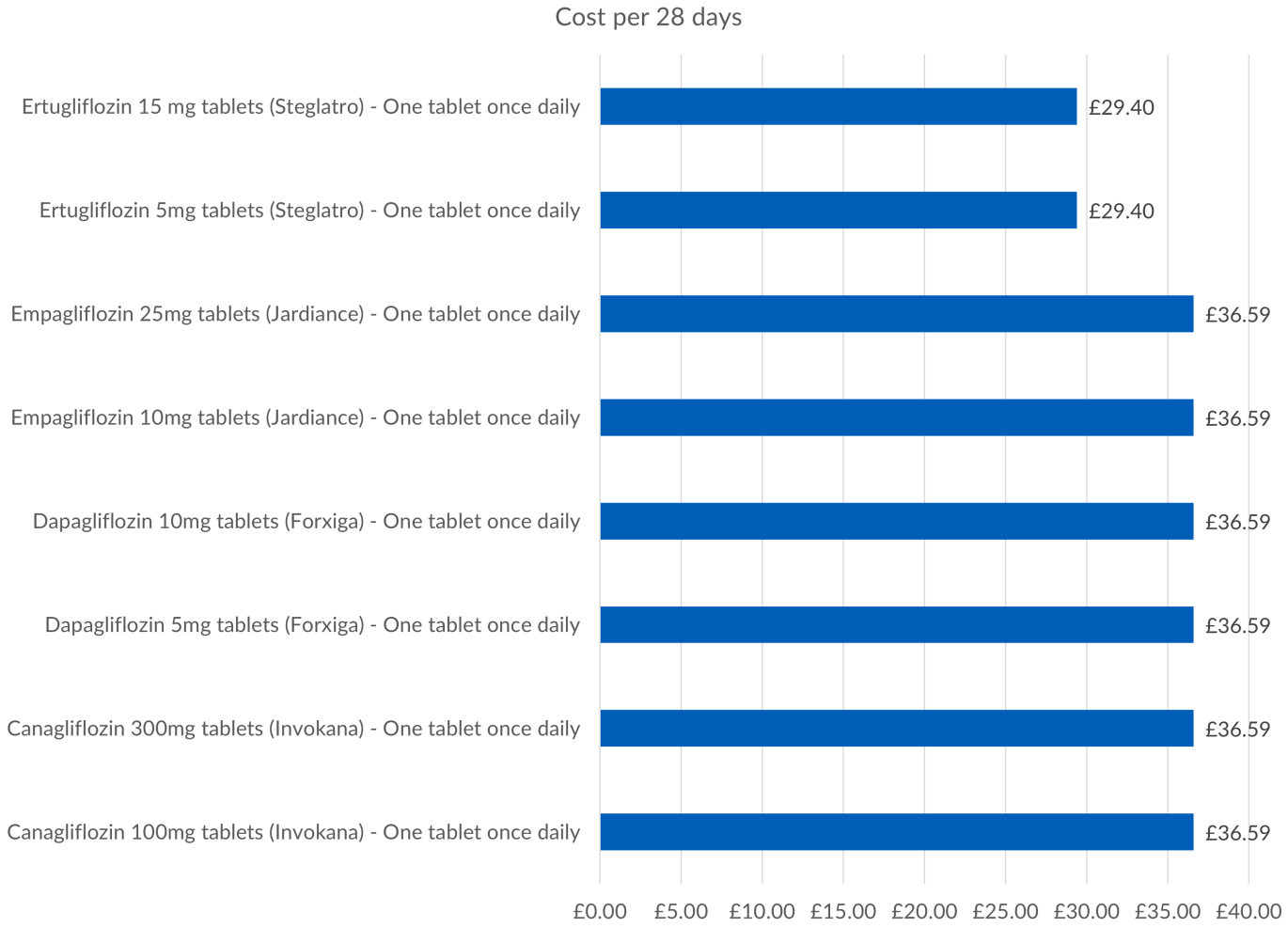
Use the least costly metformin preparation (metformin 500mg, 850mg, MR 500mg, MR 750mg, MR 1g tablets) that is suitable for the individual which achieves the desired dose. Switching 50% patients to the least costly metformin preparations could save £24.5 million across England and Wales. This equates to £34,524 per 100,000 population.

SGLT2 inhibitors

Around £81.6 million is spent on SGLT2 inhibitors across England, Wales and Scotland.

Ertugliflozin is the least costly SGLT2 inhibitor at £29.40 per 28 days and is 20% less costly that canagliflozin, dapagliflozin and empagliflozin which all cost £36.59 for 28 days, but there is a greater uncertainty around the cardiovascular benefits associated with ertugliflozin currently.[6,16]

Chart 2: SGLT2 inhibitors cost comparison[15,16]



If appropriate for the individual, switching 25% of patients on SGLT2 inhibitors to ertugliflozin could save £14.9 million annually across England and Wales. This equates to £20,901 per 100,000 population.

DPP-4 inhibitors

Across England, Wales and Scotland, approximately £58.7 million is spent on saxagliptin, sitagliptin, vildagliptin, linagliptin and combination products with metformin.

Chart 3: DPP-4 inhibitors cost comparison[15,16]

Currently the least costly DPP-4 inhibitor is alogliptin which costs £26.60 for 28 days treatment with all strengths (6.25mg, 12.5mg and 25mg). The combination product of alogliptin 12.5mg and metformin 1g also costs £26.60 for 28 days treatment.[16] Although alogliptin is the least costly DPP-4 inhibitor this could change when generic versions become available. It may take several months for generic versions to reach the market. The following are the latest information regarding patent expiry dates:[36]

- Sitagliptin – 22 September 2022
- Vildagliptin – 27 September 2022
- Vildagliptin and metformin – 15 November 2022
- Sitagliptin and metformin – 7 April 2023
- Saxagliptin - 4 October 2024
- Linagliptin – 29 August 2026

If generic versions of sitagliptin and vildagliptin become available at a reduced cost compared to the branded versions, then this could provide significant savings. A 25% reduction in spend on sitagliptin and vildagliptin, could release savings of £19.8 million across England and Wales. This equates to £27,832 per 100,000 population.

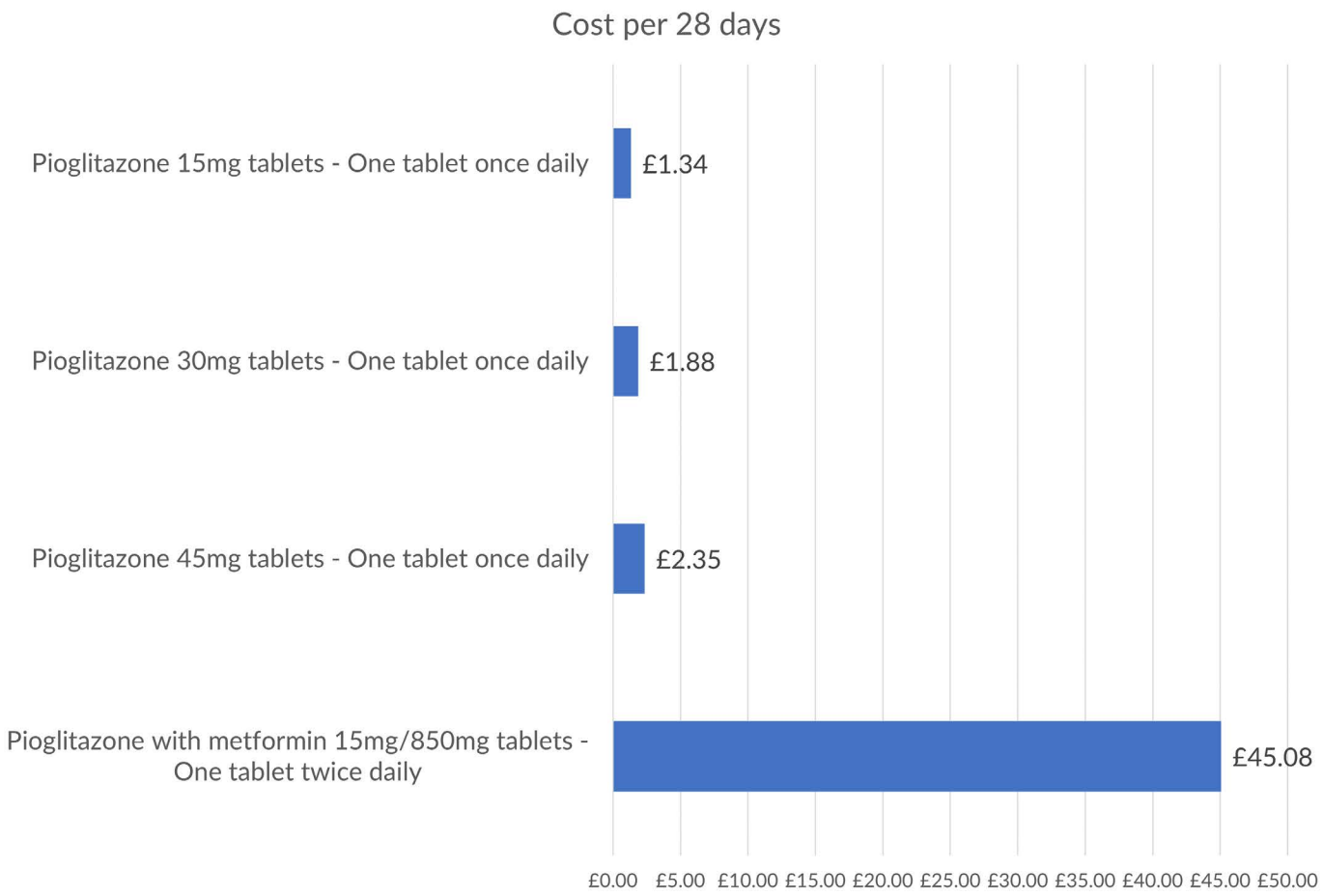
DPP-4 inhibitors have a flat pricing structure across strengths and doses should be optimised to the fewest number of tablets to be taken.[16] Strict criteria and follow-up need to be applied which may have an impact on primary care resources.

Pioglitazone

Pioglitazone is available in a combination product with standard-release metformin. Whilst this might be more convenient for patients to take, the combination product is more costly (£45.39 per 28 days) than prescribing the individual drugs (£2.54 per 28 days).[16] Review all patients on the combination product.

Across England, Wales and Scotland , approximately £208,194 is spent on pioglitazone and metformin combination product. Savings of around £351,133 annually across England and Wales or £494 per 100,000 population could be made by switching 50% of prescriptions to the single components, pioglitazone and metformin, in suitable patients.

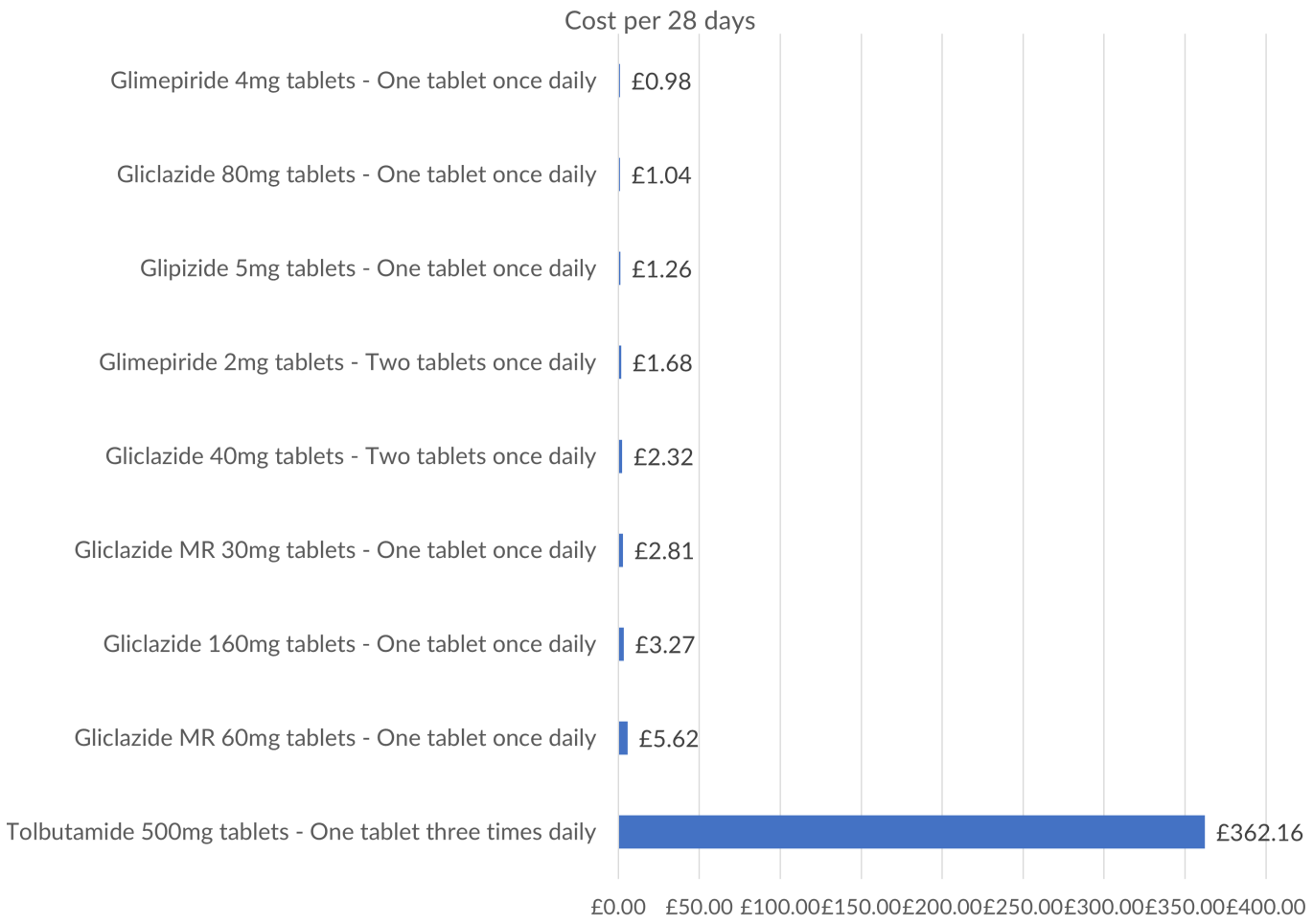
Chart 4: Pioglitazone cost comparison[15,16]



Sulfonylureas

Tolbutamide has a high acquisition cost compared to other sulfonylureas. Modified-release gliclazide 30mg and 60mg tablets are more costly than immediate release gliclazide 80mg and 160mg respectively.[16] Modified-release gliclazide 30mg tablets may be considered to be approximately equivalent in therapeutic effect to immediate release gliclazide 80mg tablets. Immediate release gliclazide may be given once daily for doses up to 160mg. Doses higher than 160mg should be given in divided doses (up to a maximum of 320mg per day).[15] It is more cost-effective to use immediate release gliclazide for doses up to 160mg of immediate release gliclazide and this dose is taken once daily. Doses above 160mg should be given in divided doses or a modified-release preparation used, taking into account the therapeutic equivalence between immediate release and modified-release gliclazide preparations.

Chart 5: Sulfonylureas cost comparison[15,16]



Savings of up to £489,444 per year across England and Wales or £688 per 100,000 population could be achieved by switching 50% of tolbutamide to gliclazide in suitable individuals.

GLP-1 receptor agonists

Approximately £68.3 million is spent on GLP-1 receptor agonists across England, Wales and Scotland.

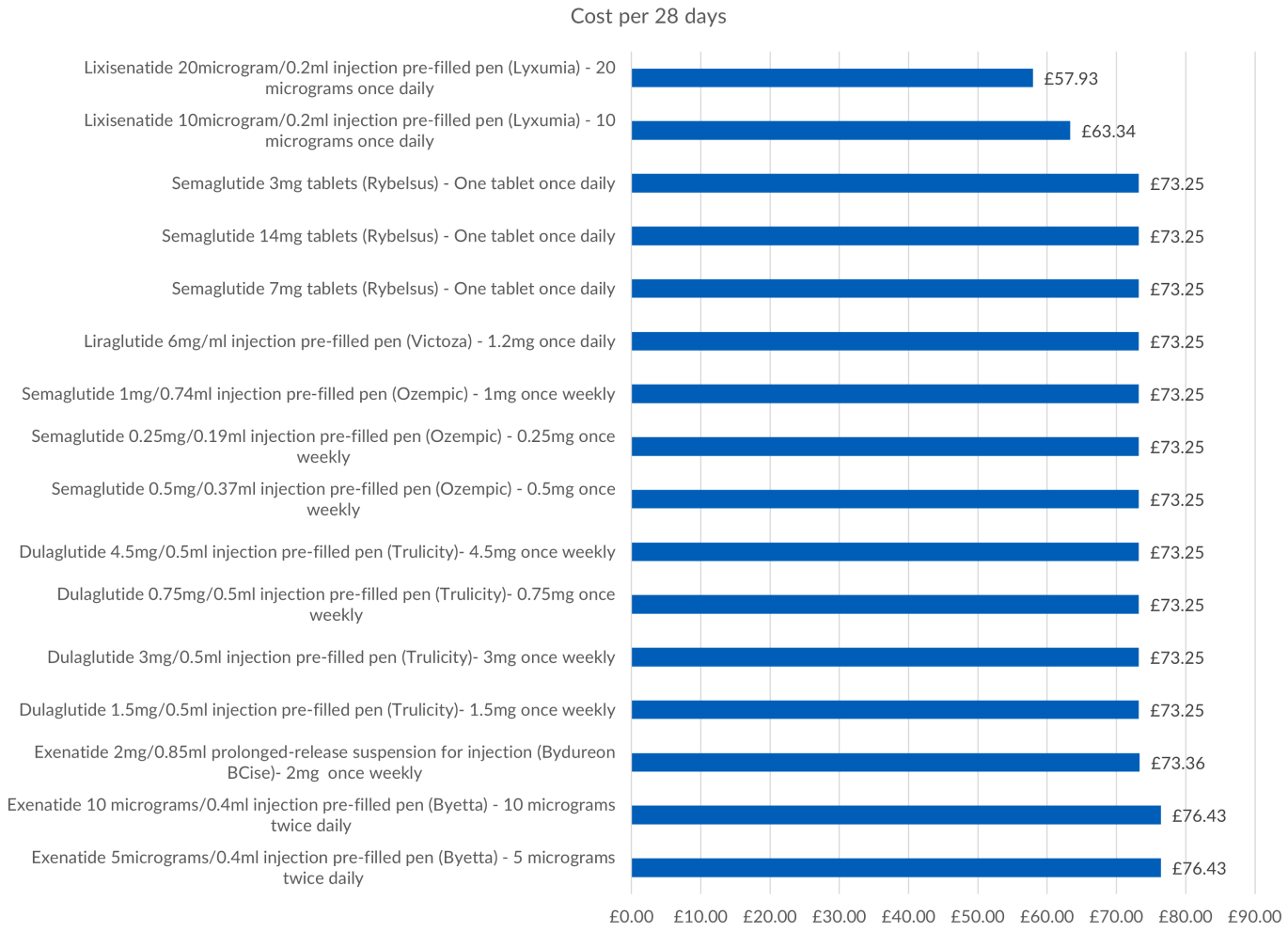
GLP-1 receptor agonist product pack sizes are sufficient for one month's supply.[15] Care needs to be taken to ensure that larger quantities are not prescribed mistakenly. Monthly prescription quantities are generally encouraged to avoid waste and for safety reasons. The PrescQIPP Hot Topic resource GLP-1 quantities helps to identify patients prescribed potential excessive amounts so that prescription quantities can be adjusted.

NICE recommends if triple therapy with metformin and two other oral drugs is not effective, not tolerated or contraindicated, then consider triple therapy by switching one drug for a GLP-1 receptor agonist for adults that:[6]

- Have a BMI of 35kg/m^2 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/m^2 and:
  - For whom insulin therapy would have significant occupational implications or
  - Weight loss would benefit other significant obesity-related comorbidities.

NICE recommend discontinuing GLP-1 receptor agonists if the person has not had a beneficial metabolic response (a reduction of at least 11mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in six months).[6]

Chart 6: GLP-1 receptor agonists cost comparison[15,16]



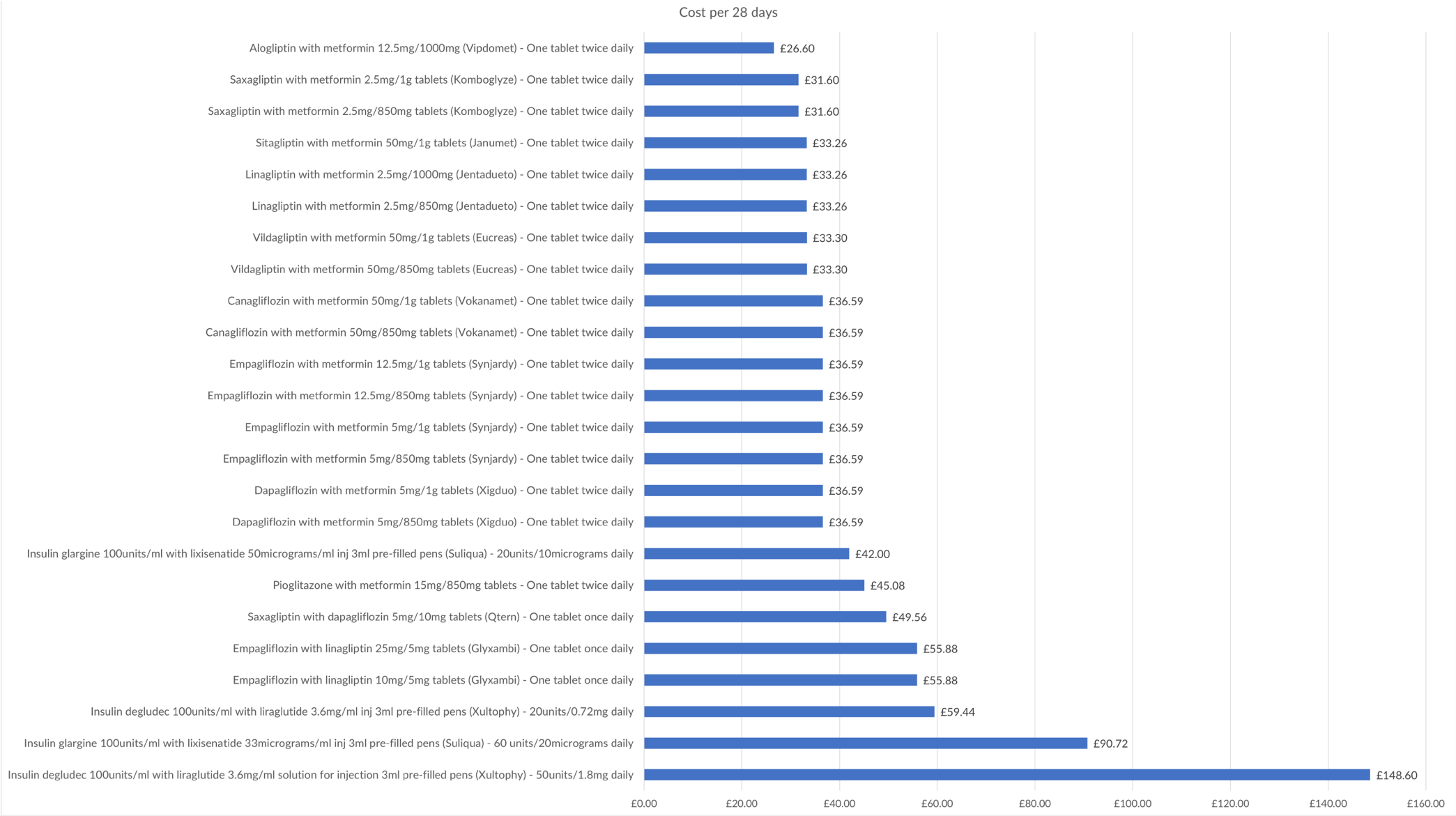
If 10% of GLP-1 receptor agonist prescriptions were discontinued in line with NICE recommendations, this would provide **annual savings of £25.2 million across England and Wales or £35,439 per 100,000 population**.

Combination products

Combination products may be more convenient for patients to take or help adherence. 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 and will therefore be inappropriate to use in any patients stabilised on a different dose. They can be less costly, the same price or more expensive than prescribing the single components:[16]

- Pioglitazone 15mg and metformin 850mg combination product costs £45.39, the two components prescribed separately costs £2.54 for 28 days treatment.
- DPP-4 inhibitor and metformin combination products are the same cost as the single components.
- The Scottish Medicines Consortium has reviewed all five of the DPP-4 inhibitor/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.[37-41]
- Canagliflozin, dapagliflozin and empaglifozin combinations with metformin cost the same as prescribing the SGLT2 inhibitor on its own and so are less costly than providing single components.
- Dapagliflozin with saxagliptin combination and empagliflozin with linagliptin combination products are less costly than providing the single components.

Chart 7: Combination products cost comparison[16]

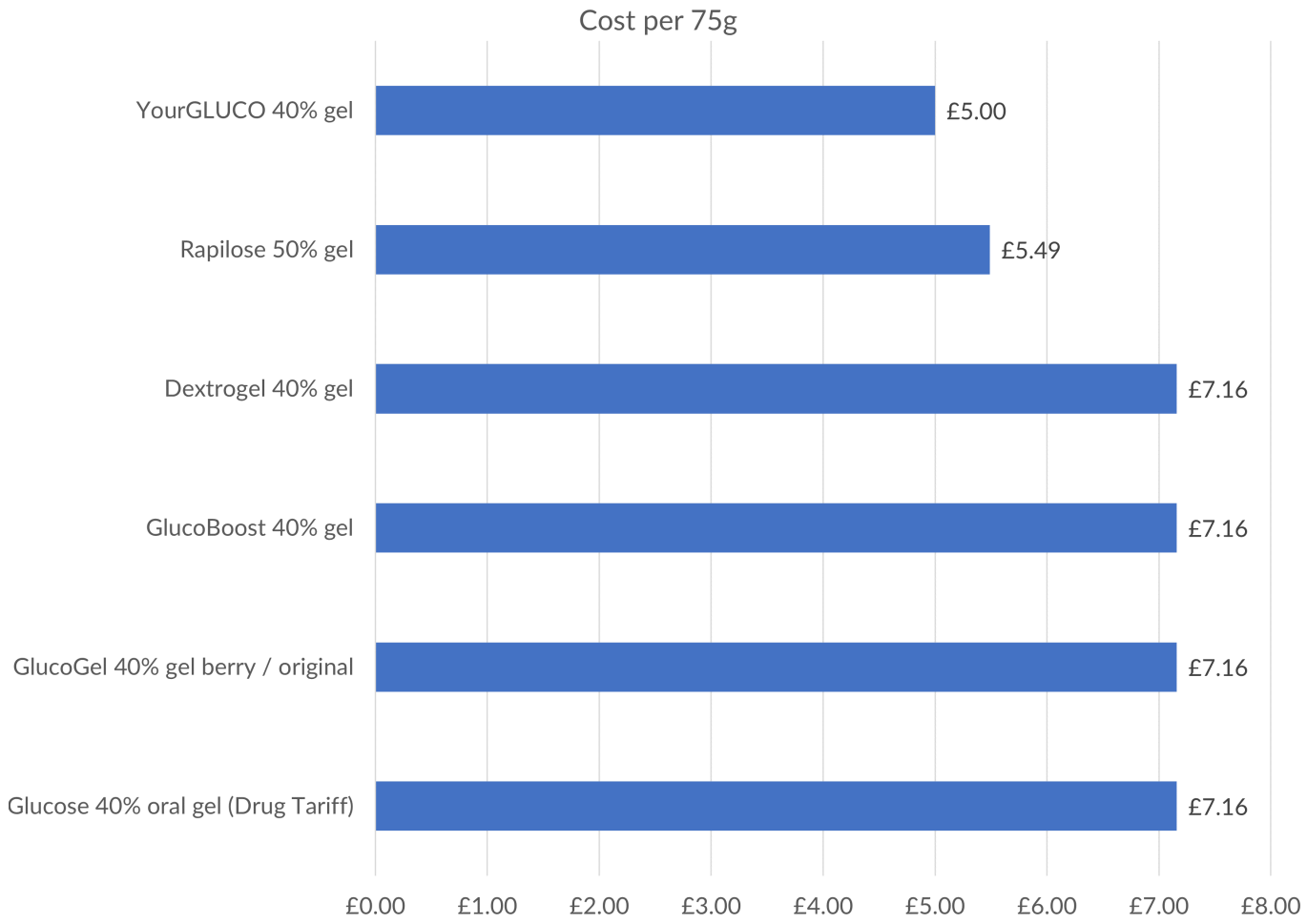


Treatment of hypoglycaemia

Self care treatment of hypoglycaemia is usually appropriate for the majority of people, as summarised in this bulletin. If clinically appropriate glucose 40% oral gel and injectable glucagon may be prescribed.

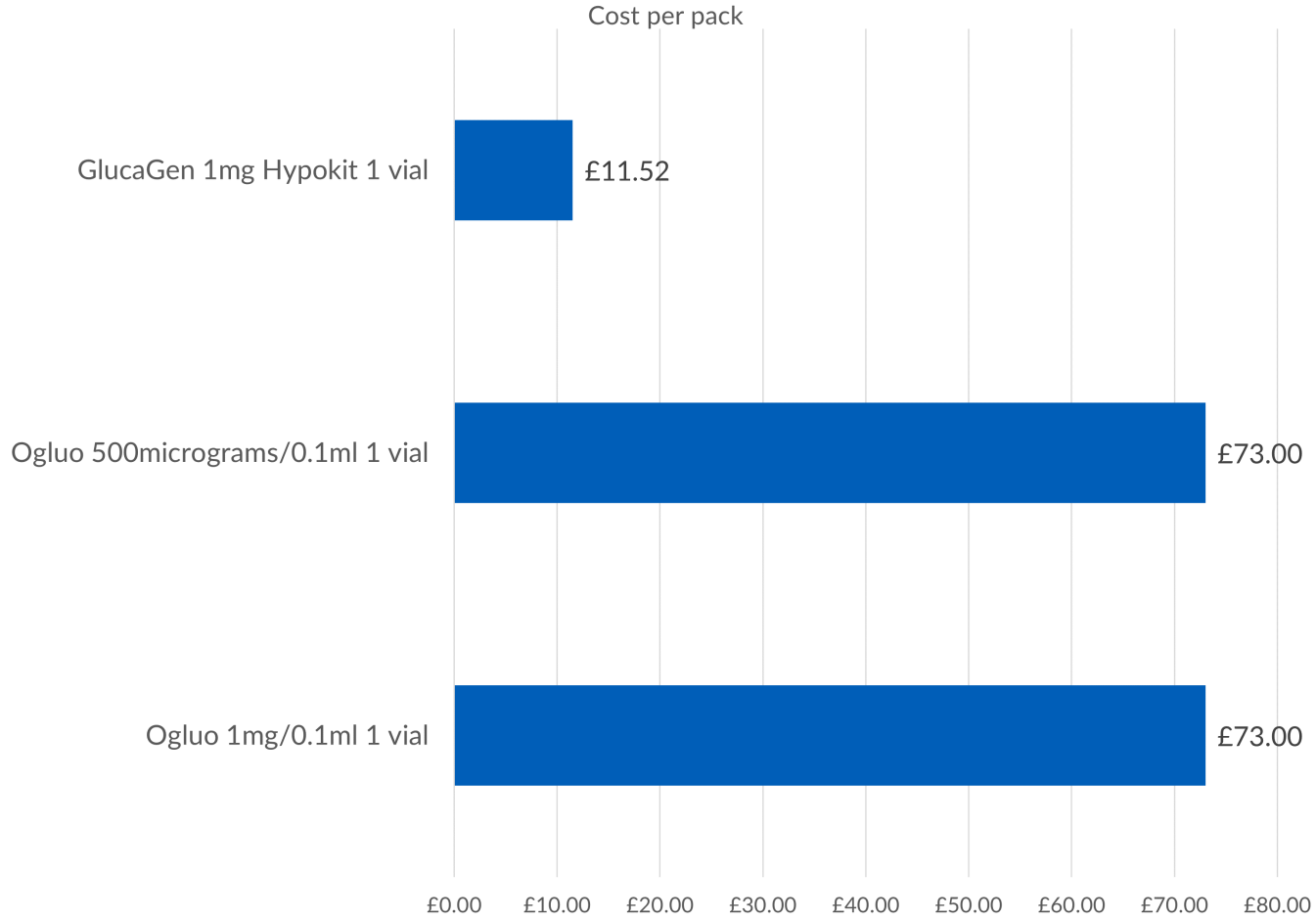
The Drug Tariff price for generically prescribed glucose 40% oral gel, GlucoBoost and GlucoGel are priced £7.16 (3 x 25g).[15,16] The most cost-effective brand is Dextrogel 40% gel which costs £4.30 (3 x 25g).[15]

Chart 8: Glucose 40% oral gel cost comparison[15,16]



Injectable glucagon hydrochloride 1mg is available as GlucaGen Hypokit powder and solvent for injection which costs £11.52 for one vial. Ogluo is a pre-filled disposable device containing glucagon 1mg/0.2mL and 500micrograms/0.1mL which both cost £73.00 for one device.[16] The most cost-effective device is GlucaGen Hypokit.

Chart 9: Glucagon injection cost comparison[16]



The Cost Comparison Charts are also available on the PrescQIPP website and the prices are updated monthly.

Summary

Structured education should be offered at diagnosis and individual lifestyle interventions such as dietary advice, weight loss, exercise, alcohol consumption and smoking status should be regularly discussed and reinforced during annual review.[6]

HbA1c targets should be agreed on an individual basis and measured every three to six months. Routine self-monitoring of capillary blood glucose should not be offered to adults with type 2 diabetes unless they meet the NICE criteria for regular testing. Certain people with type 2 diabetes on multiple daily insulin injections can be offered isCGM if in-line with NICE guidance.[6]

Initiation of oral hypoglycaemic therapy should be based on effectiveness, safety, tolerability, monitoring requirements, licensed indications, cost, individual clinical circumstances, preferences and needs.

Cardiovascular status should be assessed to determine whether the person with type 2 diabetes has chronic heart failure, established atherosclerotic CVD or are at high risk of developing CVD. Once cardiovascular status is determined treat in-line with NICE Guideline [NG28] for first-line drug treatment and further treatment options if needed as summarised in algorithm 1.

If two drugs in the same class are appropriate, choose the option with the lowest acquisition cost.[6]

The PrescQIPP diabetes webkit brings together all the PrescQIPP diabetes resources, data and showcases good practice examples of projects focusing on medicines optimisation in diabetes. Each set of resources contains tools that can be adapted for local use before implementation.

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Additional PrescQIPP resources

Briefing	https://www.prescqipp.info/our-resources/bulletins/bulletin-315-diabetes/
Implementation tools	
Data pack	https://data.prescqipp.info/?pdata.u/#/views/B315_Diabetes/FrontPage?:iid=1

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