Antihyperglycaemic Agents used for Type 2 Diabetes

Oral hypoglycaemic agents are the group of drugs that may be taken singly or in combination to lower the blood glucose in type 2 diabetes. Type 2 diabetes can be due to increased peripheral resistance to insulin or to reduced secretion of insulin. They should be used together with changes in diet and lifestyle to achieve good glycaemic control and it is customary to monitor such changes for three months before considering medication. Oral hypoglycaemic agents are not usually used in type 1 diabetes but metformin may be of use in combination with insulin for overweight people with type 1 diabetes. [1]

Blood glucose-lowering therapy [2]

HbA1c measurement
In adults with type 2 diabetes, measure HbA1c levels at:

- 3- to 6-monthly intervals (tailored to individual needs), until the HbA1c is stable on unchanging therapy
- 6-monthly intervals once the HbA1c level and blood glucose-lowering therapy are stable.

If HbA1c monitoring is invalid because of disturbed erythrocyte turnover or abnormal haemoglobin type, estimate trends in blood glucose control using one of the following:

- Quality-controlled plasma glucose profiles.
- Total glycated haemoglobin estimation (if abnormal haemoglobins).
- Fructosamine estimation.

HbA1c targets
For adults with type 2 diabetes managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycaemia, support the person to aim for an HbA1c level of 48 mmol/mol (6.5%).

For adults on a drug associated with hypoglycaemia, support the person to aim for an HbA1c level of 53 mmol/mol (7.0%).

In adults with type 2 diabetes, if HbA1c levels are not adequately controlled by a single drug and rise to 58 mmol/mol (7.5%) or higher: reinforce advice about diet, lifestyle and adherence to drug treatment, support the person to aim for an HbA1c level of 53 mmol/mol (7.0%) and intensify drug treatment.

Consider relaxing the target HbA1c level on a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes:

- Who are unlikely to achieve longer-term risk-reduction benefits - for example, people with a reduced life expectancy
- For whom tight blood glucose control poses a high risk of the consequences of hypoglycaemia - for example:
  - People who are at risk of falling.
  - People who have impaired awareness of hypoglycaemia.
  - People who drive or operate machinery as part of their job.
- For whom intensive management would not necessarily be appropriate - for example people with significant comorbidities.
If adults with type 2 diabetes achieve an HbA1c level that is lower than their target and they are not experiencing hypoglycaemia, encourage them to maintain it. Be aware that there are other possible reasons for a low HbA1c level - for example, deteriorating renal function or sudden weight loss.

**Rescue therapy at any phase of treatment**
If an adult with type 2 diabetes is symptomatically hyperglycaemic, consider insulin or a sulfonylurea and review treatment when blood glucose control has been achieved.

**Step 1 - initial drug treatment**
Offer standard-release metformin as the initial drug treatment for adults with type 2 diabetes. Gradually increase the dose over several weeks to minimise the risk of gastrointestinal side-effects. If an adult with type 2 diabetes experiences gastrointestinal side effects with standard-release metformin, consider a trial of modified-release metformin.

In adults with type 2 diabetes, review the dose of metformin if the eGFR is below 45 ml/minute/1.73m$^2$. Stop metformin if the eGFR is below 30 ml/minute/1.73m$^2$. Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45ml/minute/1.73m$^2$.

If metformin is contra-indicated or not tolerated, consider initial drug treatment with a dipeptidyl peptidase-4 (DPP-4) inhibitor or pioglitazone or a sulfonylurea. Do not offer or continue pioglitazone if they have any of the following:

- Heart failure or history of heart failure.
- Hepatic impairment.
- Diabetic ketoacidosis (DKA).
- Current, or a history of, bladder cancer.
- Uninvestigated macroscopic haematuria.

**Step 2**
If initial drug treatment with metformin has not continued to control HbA1c to below the person's individually agreed threshold for intensification, consider dual therapy with:

- Metformin and a DPP-4 inhibitor; or
- Metformin and pioglitazone; or
- Metformin and a sulfonylurea.

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

- DPP-4 inhibitor and pioglitazone; or
- DPP-4 inhibitor and a sulfonylurea; or
- Pioglitazone and a sulfonylurea.

Treatment with combinations of medicines including sodium-glucose cotransporter 2 (SGLT-2) inhibitors may be appropriate for some people with type 2 diabetes.

**Step 3**
If dual therapy with metformin and another oral drug has not continued to control HbA1c to below the person's individually agreed threshold for intensification, consider either:

**Triple therapy with:**

- Metformin, a DPP-4 inhibitor and a sulfonylurea; or
- Metformin, pioglitazone and a sulfonylurea; or
- Starting insulin-based treatment.
If triple therapy with metformin and two other oral drugs is not effective, not tolerated or contra-indicated, consider combination therapy with metformin, a sulfonylurea and a glucagon-like peptide-1 (GLP-1) mimetic for adults with type 2 diabetes who:

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

Only continue GLP-1 mimetic therapy if there is a beneficial metabolic response (a reduction of at least 11 mmol/mol (1.0%) in HbA1c and a weight loss of at least 3% of initial body weight in six months).

In adults with type 2 diabetes, if metformin is contra-indicated or not tolerated and if dual therapy with two oral drugs has not continued to control HbA1c to below the person’s individually agreed threshold for intensification, consider insulin-based treatment.

Only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team.

Treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with type 2 diabetes.

- Dapagliflozin is recommended as a treatment option if used with metformin or with insulin (with or without any other antidiabetic drugs).\(^3\)
- Using either canagliflozin or empagliflozin is recommended as an option for treating type 2 diabetes:\(^4, 5\)
  - In combination with metformin but only if a sulfonylurea is contra-indicated or not tolerated, or the person is at significant risk of hypoglycaemia or its consequences.
  - In a triple therapy regimen as an option for treating type 2 diabetes in combination with:
    - Metformin and a sulfonylurea; or
    - Metformin and a thiazolidinedione.
  - In combination with insulin with or without other antidiabetic drugs.

**Metformin**

The dose of metformin should be stepped up over several weeks to minimise the risk of gastrointestinal side-effects. Gastrointestinal side-effects occur commonly with metformin at higher doses and may necessitate a change of drug. A trial of extended-absorption metformin may be used if gastrointestinal tolerability prevents the person from continuing with metformin. There is no evidence that metformin is associated with an increased risk of lactic acidosis, or with increased levels of lactate, compared to other antihyperglycaemic treatments.\(^6\)

**Insulin secretagogues**

**Sulfonylureas**

Sulfonylureas are thought to act by enhancing pancreatic islet cell function. They are also thought to act on the liver, stimulating the glycolytic pathway and inhibiting the production of glucose. They generally have a duration of action of 12-24 hours.

- **Benefits and indications:**
  - Newer drugs in this group, such as glipizide and gлимipramide, appear to afford similar efficacy as the older drugs such as gliclazide.
  - Chlorpropamide is no longer recommended, as it has more side-effects than other members of this group.
Risks:
- The main risk with sulfonylureas is hypoglycaemia. This is increased in older age groups, mild-to-moderate hepatic impairment and renal impairment.
- Glibenclamide, a long-acting sulfonylurea, is associated with a greater risk of hypoglycaemia and therefore should be avoided in the elderly; shorter-acting alternatives, such as gliclazide or tolbutamide, should be used instead.
- Other problems can include weight gain, liver dysfunction and gastrointestinal disturbance.

Rapid-acting insulin secretagogues - postprandial glucose regulators
The two meglitinides licensed for use in the UK are repaglinide and nateglinide. They are relatively short-acting stimulators of insulin secretion (<6 hours). They act by binding to various sites on pancreatic beta cells.

- Benefits and indications:
  - Meglitinides are characterised by short duration and rapid onset of action, which requires them to be taken before a main meal.
  - Repaglinide may be suitable as monotherapy for non-obese patients in whom metformin is contra-indicated or not tolerated, or in combination with metformin.
  - Nateglinide is licensed only for use in combination with metformin.

- Risks: as with the sulfonylureas, the main risk with meglitinides is hypoglycaemia.

Thiazolidinediones
Thiazolidinediones (TDZs) or 'glitazones' - pioglitazone is the only one currently licensed in the UK. Its mechanism of action is still subject to debate but is thought to act in a similar manner to metformin, increasing hepatic sensitivity to insulin, and enhancing glucose clearance. Unlike metformin, it appears to have an effect on insulin-mediated glucose uptake at all insulin levels, making it effective in patients with insulin resistance.

- Benefits and indications:
  - TDZs are usually used in combination with a sulfonylurea or metformin. It has also been licensed as monotherapy.
  - The combination with metformin or a sulfonylurea should only be used in patients unable to tolerate metformin and sulfonylurea in combination therapy, or in whom either metformin or a sulphonylurea is contra-indicated.
    - In such cases, the TDZ should replace whichever drug in the combination is poorly tolerated or contra-indicated.
    - A TDZ plus metformin is a useful combination for obese patients. The introduction of a TDZ may cause a deterioration of blood glucose control temporarily when used in combination therapy.
  - Pioglitazone may be considered with insulin therapy in patients who have previously had a marked glucose-lowering response to TDZ therapy or in those on high-dose insulin therapy and whose blood glucose is inadequately controlled.

- Risks:
  - Do not commence or continue a TDZ in patients who have heart failure, or who are at higher risk of fracture:
    - Cardiovascular: the risk of heart failure is increased when pioglitazone is combined with insulin and in patients with a history of cardiovascular disease. Patients who take pioglitazone should be closely monitored for signs of heart failure, and treatment should be stopped immediately if any deterioration in cardiac status occurs. Pioglitazone should not be used in patients with heart failure or a history of heart failure.
    - Risk of bladder cancer: there is a small increased risk of bladder cancer associated with pioglitazone use. Pioglitazone should not be used in patients with active bladder cancer, a past history of bladder cancer or for patients with uninvestigated macroscopic haematuria.
    - There have been rare reports of liver failure but large-scale trials have shown no difference in incidence between TDZs and other oral hypoglycaemics. Baseline LFTs and periodic monitoring are recommended.
    - There is an increased risk of fractures, especially in women.
**Acarbose**
- Acarbose acts by inhibiting intestinal alpha glucosidases, which delays the absorption and digestion of sucrose and starch.
- Acarbose is usually only used when other oral glucose-lowering medications cannot be used.
- The use of acarbose is limited by its gastrointestinal adverse effects but these do decrease with time.

**Dipeptidylpeptidase-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin)**
- Linagliptin, saxagliptin, sitagliptin, and vildagliptin inhibit dipeptidylpeptidase-4 to increase insulin secretion and lower glucagon secretion.
- Linagliptin is licensed for use in type 2 diabetes as monotherapy (if metformin is inappropriate), or in combination with metformin when metformin alone provides inadequate glucose control, or with both metformin and a sulfonylurea (when additional treatment is required).
- Saxagliptin, sitagliptin, and vildagliptin are licensed for use in combination with metformin, a sulfonylurea (if metformin is inappropriate) or pioglitazone when additional treatment is required.
- Sitagliptin and vildagliptin are licensed for use as monotherapy (if metformin is inappropriate).
- Sitagliptin is licensed for use in combination with metformin and a sulfonylurea, or with both metformin and pioglitazone when dual therapy fails to achieve adequate glycaemic control.
- Sitagliptin or saxagliptin in combination with insulin (with or without metformin) is licensed for use when insulin has not provided adequate glycaemic control.

**Benefits and indications:**
- They may be appropriate ahead of a TDZ when the latter is contra-indicated, or if further weight gain would cause or exacerbate significant problems associated with a high body weight. In these circumstances, they are considered as a third-line therapy in combination with metformin and sulfonylurea when glycaemic control is still inadequate.
- They can be considered second-line with metformin in patients at particular risk of hypoglycaemia (elderly patients living alone; other patients working at heights or with heavy machinery), or second-line in combination with a sulfonylurea in patients intolerant of metformin.

**Risks:**
- Hypersensitivity reactions may occur (anaphylaxis, angio-oedema and Stevens-Johnson syndrome).

Only continue DPP-4 inhibitor therapy if there has been a beneficial metabolic response (HbA1c falling 0.5% in six months).

**Glucagon-like peptide-1 mimetics (exenatide, liraglutide, and lixisenatide)**
Exenatide and liraglutide are both given by subcutaneous injection. There is a once weekly treatment option. They activate the GLP-1 receptor to increase insulin secretion, suppress glucagon secretion and slow gastric emptying. Treatment is associated with the prevention of weight gain and possibly even with weight loss.[7]

**Benefits and indications:**
- It may be a particularly useful step in patients who hold LGV or PCV driving licences, who would lose them if converted to insulin.
- Can cause significant weight loss (rather than gain). Hence, it is most appropriate in patients with BMI ≥35.0 kg/m².
• Risks:
  • May cause significant gastrointestinal disturbance and there are reports of associated severe acute pancreatitis.
  • There is an interaction with warfarin (monitor INR carefully).
  • The long-term safety is not yet established.

Only continue GLP-1 mimetic treatment if there has been a beneficial response (HbA1c fall of 1% and a weight loss of at least 3% of initial body weight at six months).

Sodium-glucose co-transporter 2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin)

SGLT-2 inhibitors reduce glucose reabsorption in the renal proximal convoluted tubule and increase urinary glucose excretion. Canagliflozin, dapagliflozin, and empagliflozin are licensed for use in type 2 diabetes as monotherapy (if metformin is inappropriate), or in combination with insulin or other antidiabetic drugs (if existing treatment fails to achieve adequate glycaemic control). Dapagliflozin is not recommended in combination with pioglitazone.

Serious and potentially life-threatening cases of DKA have been reported in patients taking SGLT-2 inhibitors for type 2 diabetes. [7]

Clinical Editor’s notes (July 2017)
Dr Hayley Willacy would like to draw your attention to the CANVAS programme, which integrated data from two trials involving people with type 2 diabetes, the majority of whom had an elevated risk of cardiovascular disease. [9] Participants in each trial were randomly assigned to receive canagliflozin or placebo and were followed for a mean of 188.2 weeks. Those receiving canagliflozin had a lower risk of cardiovascular events than those who received placebo; there was also a reduced risk of progression of renal disease, but a greater risk of amputation, primarily at the level of the toe or metatarsal.

Further reading & references

- Management of diabetes; Scottish Intercollegiate Guidelines Network - SIGN (March 2010)
- Diabetes UK
- Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes; NICE Technology appraisal (May 2016)

1. Type 1 diabetes in adults: diagnosis and management; NICE Guidelines (August 2015)
2. Type 2 diabetes in adults: management; NICE Guidelines (December 2015)
3. Dapagliflozin in combination therapy for treating type 2 diabetes; NICE Technology Appraisal Guidance, June 2013
4. Canagliflozin in combination therapy for treating type 2 diabetes; NICE Technology Appraisal Guidance, June 2014
5. Empagliflozin in combination therapy for treating type 2 diabetes; NICE Technology Appraisal Guidance, March 2015
7. British National Formulary; NICE Evidence Services (UK access only)

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