

Glucose management in Type 2 Diabetes in Adults

The natural history of type 2 diabetes is for HbA1c to deteriorate with time. A stepwise approach to treatment is necessary. Not all steps will be appropriate to all patients. Patients who are highly symptomatic, or where control is worsening rapidly, may need to move up the steps more quickly or go straight to insulin treatment.

OHA = oral hypoglycaemic agent. See sections on individual drugs for indications and contraindications of each drug.

HbA1c Measurement

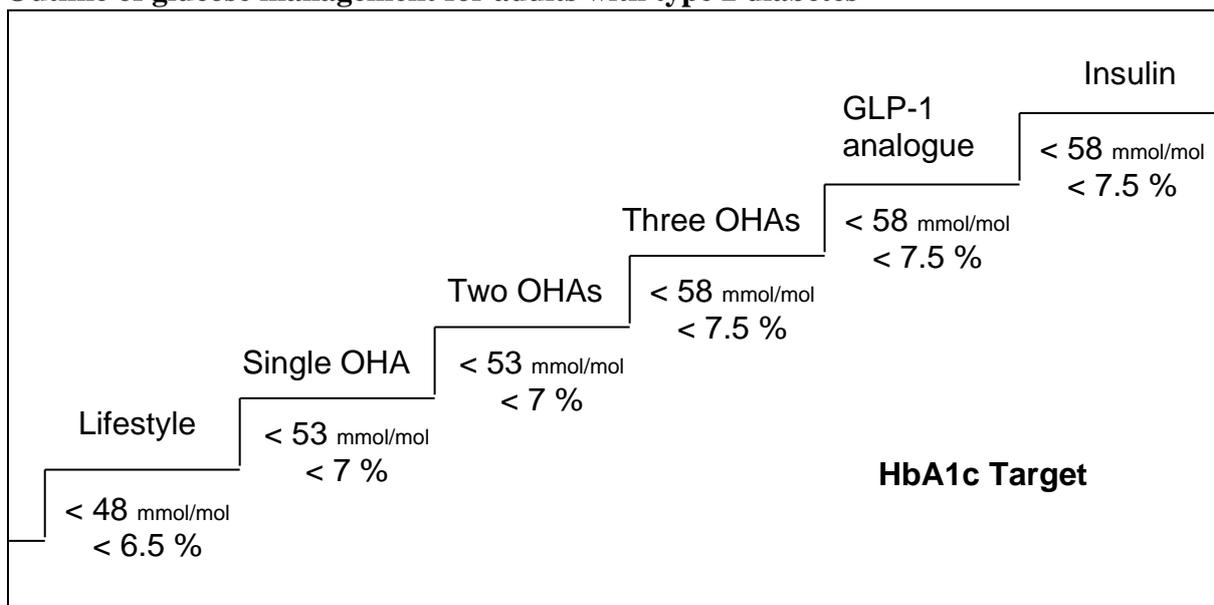
HbA1c should be measured every 3 months if treatment has been changed or every 6 months if target HbA1c has been met and no changes to treatment made. Please remember that these HbA1c targets are general guidelines, which need to be adapted to each person individually. Targets may be more relaxed in those with other health problems and old age if appropriate.

On average, only expect an 11 mmol/mol (1%) fall in HbA1c when introducing at full dose any OHA.

If HbA1c > 53 mmol/mol (7.0%), substitution of one OHA for another is unlikely to improve glycaemic control. The new OHA needs to be added to existing treatment.

In patients with abnormal haemoglobins (e.g. sickle cell disease) or with increased haemoglobin turnover (e.g. anaemia), HbA1c is not always an accurate reflection of glycaemic control.

Outline of glucose management for adults with type 2 diabetes



Hypoglycaemia “at risk” patients

Patients at risk of severe hypoglycaemia should have higher HbA1c targets. These include patients on insulin or a sulphonylurea who have:

- Long duration of diabetes
- Hypoglycaemia unawareness
- Elderly patients
- Patients with impaired renal function

These patients should have an HbA1c of at least 53 mmol/mol (7%). HbA1c targets should be relaxed even further if there is frequent hypoglycaemia or lab glucose < 4 mmol/l. There is no evidence of benefit (and some evidence of harm) for tight glycaemic control in elderly patients.

Step 1: Lifestyle

- All patients should be given advice on healthy diet and exercise.
- Overweight patients should be advised on weight reduction.
- Newly diagnosed patients should be encouraged to attend Diabetes Education sessions (DES). Please confirm diagnosis of diabetes before attendance and take baseline HbA1c.
- HbA1c will then be measured prior to the third education session.
- HbA1c should be measured every 3-6 months after this.
- If HbA1c > 48 mmol/mol (6.5%), go to step 2.

Step 2: Single Oral Hypoglycaemic Agent (OHA)

- Advice on diet, exercise and weight loss (if appropriate) should be repeated.
- **Metformin** is the drug of choice in most patients.
- Glucophage SR should be used if standard release metformin causes unacceptable GI upset.
- A Sulphonylurea, Gliptin or SGLT2 inhibitor are alternative single agents.
- Pioglitazone, Acarbose or Repaglinide may occasionally be used.
- Whichever drug is started should be titrated up to the maximum tolerated dose.
- Measure HbA1c every 3-6 months.
- If HbA1c >53 mmol/mol (7%), go to step 3.

Step 3: Two Oral Hypoglycaemic Agents

- Advice on diet, exercise and weight loss (if appropriate) should be repeated.
- The second OHA added will depend on indications, contraindications and the first OHA. Possible combinations are:
 - Metformin + Sulphonylurea
 - Metformin + Gliptin
 - Metformin + Glitazone
 - Metformin + Non- Sulphonylurea secretagogue
 - Sulphonylurea + Gliptin
 - Sulphonylurea + Glitazone
 - Glitazone + Gliptin
 - Metformin + SGLT2 inhibitor
 - Sulphonylurea + Dapagliflozin
 - Gliptin + Dapagliflozin
- Whichever second drug is started should be titrated up to the maximum tolerated dose.
- Measure HbA1c every 3-6 months.
- If HbA1c >53 mmol/mol (7%), go to step 4.

Step 4: Three Oral Hypoglycaemic Agents

- Advice on diet, exercise and weight loss (if appropriate) should be repeated.
- If 2 OHA have not been sufficient, triple therapy may be considered.
- Possible combinations are:
 - Metformin + Sulphonylurea + Glitazone
 - Metformin + Sulphonylurea + Gliptin
 - Metformin + Sulphonylurea + SGLT2 inhibitor
 - Metformin + Gliptin + Dapagliflozin
 - Sulphonylurea + Gliptin + Dapagliflozin
- Whichever third drug is started should be titrated up to the maximum tolerated dose.
- For patients who cannot take metformin or a sulphonylurea go straight to step 5.
- Measure HbA1c every 3-6 months.
- If HbA1c >58 mmol/mol (7.5%), go to step 5.

Step 5: GLP-1 Analogue

- Advice on diet, exercise and weight loss should be repeated.
- Exenatide and Liraglutide are suitable for selected patients (NICE clinical guideline 66: BMI > 35 kg/m², specific problems of a psychological, biochemical or physical nature arising from high body weight, HbA1c > 7.5% (58 mmol/mol) on conventional agents). For other patients go straight to step 6.
- HbA1c and weight should be measured every 3-6 months.
- If HbA1c does not fall by 11mmol/mol (1%) at 6 months, go to step 6.
- If weight does not fall by 5% at 12 months, go to step 6.

Step 6: Insulin

- Advice on diet, exercise and weight loss (if appropriate) should be repeated.
- Insulin regimen depends on patient preference and pattern of blood glucose readings.
- Metformin is usually continued with insulin.
- Most patients on once daily insulin will require OHA to cover meal time glucose excursions.
- Common insulin regimens in type 2 diabetes are:
 - Twice daily mixed insulin with metformin
 - Once daily long acting insulin with metformin ± sulphonylurea
 - Basal-bolus insulin ± metformin
- Measure HbA1c every 3-6 months.
- Target HbA1c is < 58 mmol/mol (7.5%) but remember this target may not be appropriate in those with other health problems or in the elderly.

Notes on individual treatment options

1. Diet and exercise

- In the newly diagnosed patient, on average expect 11-22 mmol/mol (1-2%) fall in HbA1c with diet and exercise.
- High glucose levels at diagnosis often cause anxiety. We recommend:
 - If positive for urine ketones, refer to DNS by phone urgently.
 - If plasma glucose ≥ 30 mmol/l, refer to hospital diabetes team within 24 hours as insulin may be required.
 - If plasma glucose 15-29 mmol/l, and no urine ketones, start diet and urine testing and review patient in 2-5 days and then commence OHA.

2. Metformin

Mode of action	Improves insulin sensitivity
Effect on weight	Neutral
Indications	Patients with BMI >22 kg/m ² or as an additional agent
Contraindications and cautions	Renal impairment (creatinine > 150, eGFR < 40) severe heart failure
Onset of action	2-3 days
Common side effects	Nausea and diarrhoea S/E are lessened by starting at a low dose and increasing slowly Taking Metformin during a meal, rather than before can minimize S/E
Dose	Initially 500mg od, increased gradually to either 850mg tds or 1g bd

Note on SR metformin:

Metformin SR has less GI side effects than standard metformin. The dose is equivalent but the tablets should be given together with the evening meal. Maximum dose 2g od.

Tablets are now available in 500mg, 750mg and 1g strengths. 2 x 750mg tablets are cheaper than 3 x 500mg tablets.

Note on liquid metformin:

Metformin is also available in a liquid form for patients who have difficulties swallowing the large tablets.

3. Sulphonylureas

Mode of action	Stimulates insulin production		
Effect on weight	Weight gain common		
Indications	Patients with BMI < 22 kg/m ² or as an additional agent		
Contraindications and cautions	Severe hepatic impairment, pregnancy and lactation Decrease dose in renal impairment		
Onset of action	1-3 days		
Common side effects	Risk of hypoglycaemia		
Dose	Drug	Start	Maximum
	Gliclazide	40-80 mg daily	160 mg twice daily
	Gliclazide MR	30 mg daily	120 mg daily
	Glipzide	5 mg daily	15 – 20 mg daily
	Glimepiride	1 mg daily	6 mg daily

- There is no benefit of substituting one sulphonylurea for another
- 30mg of Gliclazide MR is equivalent to 80mg of standard release Gliclazide. The MR tablets can help compliance in some patients.
- Glibenclamide is not recommended because of the higher risk of hypoglycaemia, especially in the elderly.

4. Non sulphonylurea secretagogues

Repaglinide and Nateglinide stimulate pancreatic insulin production. Repaglinide is licensed as monotherapy or in combination with metformin. Nateglinide is only licensed in combination with metformin. Both drugs have a rapid onset and short duration of action and need to be administered shortly before each meal. They are also more expensive than Sulphonylureas and are not usually recommended.

5. Acarbose

Acarbose inhibits intestinal alpha glucosidases and therefore slows absorption of sucrose and complex carbohydrates. It is expensive with a high incidence of gastrointestinal side effects and is not usually recommended.

6. Pioglitazone

Mode of action	Improves insulin sensitivity
Effect on weight	Weight gain common
Indications	Patients unable to tolerate other agents or as an add on agent but unlikely to be effective if BMI < 22kg/m ² Patients with fatty liver
Contraindications and cautions	Heart failure, fluid retention or significant liver dysfunction, pregnancy and lactation, bladder cancer or haematuria, macular oedema. Do not prescribe initially if ALT >100 – investigate for Liver disease. A high ALT secondary to fatty liver will improve with Glitazone treatment Pioglitazone is now the only recommended glitazone.
Onset of action	Slow and may be up to 3 months to see full effect
Common side effects	Weight gain, fluid retention, anaemia
Dose	Start at 15-30mg and increase every 4 weeks to maximum 45mg

- Some patients do not respond to Pioglitazone treatment. If there is no decrease in HbA1c after 6 months, stop Pioglitazone and review other options.
- Pioglitazone is also available as a combined tablet with metformin (Competact).

7. Gliptins

Mode of action	Enhances incretin stimulated pancreatic insulin production and islet cell hyperplasia
Effect on weight	Neutral
Indications	Patients unable to tolerate other agents or as an add on agent Patients in whom weight gain is particularly undesirable
Contraindications and cautions	Previous severe hypersensitivity reaction to any drug, pregnancy or lactation, heart failure.
Onset of action	2-3 days
Common side effects	Headache, diarrhoea, URTI. May affect digoxin levels (monitor). Abnormal liver function with Vildagliptin. Risk of heart failure with Alogliptin and Saxagliptin.
Dose	Sitagliptin: 100mg od (50mg if GFR <50, 25mg if GFR <30) Saxagliptin 5mg od (2.5 mg if GFR <50, stop if GFR <15) Vildagliptin 50 mg bd (50 mg od only with SU or if GFR <50) Linagliptin 5mg od (no dose reduction in renal disease) Alogliptin 25mg od (12.5 mg if GFR <60, 6.25 mg if GFR <30)

- NICE Guideline 28 (December 2015) recommends a gliptin:
 - As monotherapy if metformin is contraindicated or not tolerated
 - In combination with metformin, pioglitazone or a sulphonylurea
- Sitagliptin appears safer than Vildagliptin.

8. SGLT2 inhibitors

Mode of action	Cause glycosuria
Effect on weight	Encourage weight loss
Indications	Patients unable to tolerate metformin or as add on to insulin or metformin. Dapagliflozin should not be used with pioglitazone.
Contraindications and cautions	Dehydration (avoid if patient on diuretic), hypotension, age >75, eGFR <60 (dapagliflozin and empagliflozin) or <45 (Canagliflozin)
Onset of action	1-3 days
Common side effects	Urinary tract infection, genital infection, dysuria, polyuria, thirst, dyslipidaemia, constipation, back pain, hypotension, dehydration
Dose	Dapagliflozin 10mg od (5mg od in liver disease) Empagliflozin 10-25mg od Canagliflozin 100-300mg od (max 100mg od if eGFR < 60)

- NICE Health Technology Appraisal 390 (May 2016) recommends SGLT2 inhibitors:
 - As monotherapy if:
 - Metformin is not tolerated or contra-indicated
 - A DPP4 inhibitor would otherwise be used
 - SU or pioglitazone not appropriate
 - As add on therapy to other glucose lowering agents including insulin
- Canagliflozin has been associated with an increased risk of lower limb amputation. This has not been seen with Dapagliflozin or Empagliflozin

9. GLP-1 Analogues

Mode of action	Enhances pancreatic insulin production and islet cell hyperplasia, increases satiety
Effect on weight	Encourages weight loss
Indications	Patients with suboptimal HbA1c despite maximal tolerated OHAs Patients with BMI > 35 kg/m ²
Contraindications and cautions	Severe GI disease, renal impairment (avoid liraglutide if GFR < 60 ml/min/1.73 m ² , Bydureon if GFR < 50 ml/min/1.73 m ² and Exenatide if GFR < 30 ml/min/1.73 m ²), pancreatitis
Onset of action	3-5 days
Common side effects	Nausea
Dose	Exenatide: Subcutaneous injection, start at 5µg bd, if tolerated increase after 4 weeks to 10 µg bd (maintenance dose) Liraglutide: Subcutaneous injection, start at 0.6mg od, if tolerated increase after 1 week to 1.2mg od and if necessary to 1.8mg od Lixisenatide: Subcutaneous injection, start at 10mcg od, if tolerated increase after 2 weeks to 20mcg od Bydureon (SR exenatide): Subcutaneous injection, 2mg weekly Dulaglutide: Subcutaneous injection, 0.75mg weekly as monotherapy or 1.5mg weekly in combination with insulin or other hypoglycaemic drugs

- Exenatide is cheaper than Liraglutide / but requires two injections per day.
- Liraglutide is more expensive but is only once a day.
- Lixisenatide costs less than Exenatide or Liraglutide
- Bydureon is cheaper than daily exenatide but does not come in a ready to use form. Patients need to mix powder and solvent immediately prior to use.
- Dulaglutide comes in a pre-filled pen and costs the same as Bydureon

10. Insulin

- Weight gain of 1-5 kg is common, using Metformin with insulin minimizes the problem
- The regimen needs to be individualized to the patient's lifestyle and home monitoring results
- Initiating insulin treatment requires the input of a diabetes specialist nurse
- Patients are encouraged to learn to adjust their insulin treatment

11. Weight loss treatments

- All weight loss treatments should be given as part of a structured weight reduction program with advice on diet and physical activity and regular review by a dietician or practice nurse