Macleod Diabetes & Endocrine Centre
Royal Devon & Exeter Hospital

Treatment pathway for type 2 diabetes

This is a simplification of NICE NG28 (update Feb 2022). We try to ensure this guidance is accurate and up-to-date, but we can't guarantee that so you should always check the BNF entry and relevant NICE guidance when prescribing. Guidance for when drugs may be safely used in renal and hepatic impairment changes particularly frequently.

In some places we have added our own or locally-agreed recommendations.

Notes on Feb 2022 NG28 update

Significant changes in the 2021 and February 2022 NICE NG28 update are:

- **SGLT2 inhibitors for T2DM with vascular disease or risk, regardless of HbA1c**.
  - SGLT2i are recommended regardless of HbA1c in T2DM with heart failure or established arterial disease.
  - SGLT2i may be considered regardless of HbA1c in T2DM with no established arterial disease but CV risk >10%.
  - SGLT2i are therefore used like statins, but can still also be used for blood glucose control in people with no vascular disease or CV risk.
  - See "*Some comments on SGLT2-inhibitors*" later in this guideline.

- **SGLT2i for T2DM with chronic kidney disease, regardless of HbA1c**.
  - SGLT2i are recommended regardless of HbA1c if urine ACR is over 30, to be added to usual ACEI/ARB.
  - SGLT2i may be considered regardless of HbA1c if urine ACR is 3-30, to be added to usual ACEI/ARB.
  - The GFR thresholds when prescribed for CKD may differ from thresholds when prescribed purely for blood glucose control.
  - See "*Some comments on SGLT2-inhibitors*" later in this guideline.

- **Changes to use of GLP-1 agonists**.
  - No longer restricted to use with metformin and sulfonylurea.
  - It is expected that most patients will have tried triple oral therapy first.

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Simplified summary

Step 1	At diagnosis	**Lifestyle** and **diet**
Step 2	If HbA1c>48	**Metformin** alone if no CV disease and CV risk not high. **Metformin and SGLT2i** if CV disease or heart failure. Consider **metformin and SGLT2i** if high CV risk.
At any time	If CVD	Add **SGLT2i** if new heart failure or CV disease. Consider adding **SGLT2i** if new high CV risk.
At any time	If raised ACR	Add **SGLT2i** if ACR>30 despite ACEI/ARB. Consider adding **SGLT2i** if as above but ACR 3-30.
Step 3+	If HbA1c≥53-58	Add further oral drugs from choice of **sulfonylurea**, **pioglitazone**, **DPP4i** (gliptin) or **SGLT2i.**
GLP-1	If HbA1c≥53-58	If BMI>35, consider replacing one of three oral drugs with **GLP-1 mimetic.**
Insulin	If HbA1c≥53-58	Usually switch to **NPH insulin** with **metformin** (+/- **SGLT2i**).

HbA1c targets

Usual targets – NICE

- 48 mmol/mol if treated with lifestyle alone, or a single drug.
- 53 mmol/mol if on a single drug associated with hypoglycaemia (insulin or SU).
- If on a single drug, the threshold for adding a second drug is HbA1c ≥58 mmol/mol.
- 53 mmol/mol on two or more drugs or insulin.

NICE guidelines are vague as to whether the threshold for adding a third drug (or GLP-1 or insulin) is >53 or ≥58 mmol/mol. We suggest that in most cases this would be 58, but 53 in some cases e.g. younger patients.

Individualised targets, e.g. in frail or elderly patients

The benefits of tight glycaemic control occur over years to decades. Frailer or older people are less likely to benefit and more susceptible to side effects, particularly hypoglycaemia.

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In 2019, Eastern locality clinicians suggested the following:

- Mild frailty or estimated life expectancy 5-10 years – HbA1c 59-64 mmol/mol
- Moderate-severe frailty or life expectancy <5 years – HbA1c 65-74 mmol/mol
- Terminal disease or frailty – focus on symptom control

First drug

- **If no CV disease and not at high-CV risk – metformin** (or M/R metformin if GI side effects). See Devon Formulary for advice on starting dose and dose adjustment.

- **If heart failure or coronary/cerebral/peripheral arterial disease – metformin <u>and</u> SGLT2i.** Start metformin first (or M/R metformin if GI side effects). Add SGLT2i regardless of HbA1c once on maximum tolerated dose of metformin.

- **If no established disease but high cardiovascular risk – "consider" metformin <u>and</u> SGLT2i**. This softer recommendation presumably allows that some patients may prefer not to take two drugs, or have HbA1c only slightly above target, or have cardiovascular risk only slightly above threshold, or have minor contraindications to SGLT2i such as history of non-severe thrush or polyuria. Please also see "*Some comments on SGLT-2 inhibitors*" later in this guideline.

    - "High risk" is QRISK2 score >10% if aged over 40.
    - Or adult aged under 40 with one or more of: hypertension, dyslipidaemia, smoking, obesity, first-degree relative with premature CV disease.

First drug if metformin not suitable

- **If heart failure or coronary/cerebral/peripheral arterial disease – SGLT2i.**

- **If no established disease but high CV risk – "consider" SGLT2i.** We interpret this to mean SGLT2i are first choice, but less strongly recommended if there are minor contraindications such as a history of non-severe thrush or polyuria.

- **If none of the above –** sulfonylurea or pioglitazone or DPP-4 inhibitor (gliptin) or SGLT2i**.** NICE does not provide an explicit preference, but the above order is implied by the statement that SGLT2i "*are recommended only if a DPP-4 inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate*".

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Add SGLT2i for new-onset CVD or CKD, regardless of HbA1c

At any time:

- An SGLT2i is recommended if there is new heart failure or new arterial disease.
- An SGLT2i can be considered if estimated cardiovascular risk becomes "high".

- An SGLT2i is recommended if urine albumin:creatinine ratio >30 mg/mmol despite already taking the highest tolerated dose of ACEI or ARB.
- An SGLT2i can be considered if as above but ACR 3-30 mg/mmol.

An SGLT2i can be **added** if HbA1c is above target. An SGLT2i can also **replace** a drug if there is no need for intensification and particularly if there would otherwise be a risk of hypoglycaemia or other side effects.

Also see "*Some comments on SGLT2-inhibitors*" later in this guideline.

Second and third oral drugs

- Often an SGLT2i will be indicated for the reasons above.
- Otherwise – any of sulfonylurea, pioglitazone, DPP-4i (gliptin) or SGLT2i.

- Add or switch drugs up to a maximum of triple oral therapy (or dual oral therapy if metformin is contraindicated or not tolerated).

GLP-1 mimetics

If triple therapy with metformin and two other oral drugs is not effective, not tolerated or contraindicated, consider switching one drug to a GLP-1 mimetic if:

- BMI 35 or higher (adjust for ethnic group if appropriate) and specific psychological or medical problems associated with obesity, **or**
- BMI below 35 **and** insulin would have significant occupational implications **or** weight loss would benefit other obesity-related comorbidities.
- Only continue GLP-1 mimetic if HbA1c reduction of 11 mmol/mol and weight loss of at least 3% are demonstrated at 6 months.

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Which GLP-1 mimetic? Our view is that there is little to choose between weekly injectable semaglutide and dulaglutide. If for any reason a daily injection is preferred, liraglutide is suggested. Oral semaglutide has not been shown to have the same cardiovascular benefits and should only be used for patients who cannot use injected therapy.

Insulin

Consider insulin if triple therapy is ineffective, contraindicated or not tolerated.

Use insulin earlier if there is ketosis (immediate insulin therapy unless mild/transient), hyperglycaemia with weight loss, significant hyperglycaemic symptoms, or if the patient is slimmer than usual for type 2 diabetes.

When starting insulin, continue metformin unless contraindicated or not tolerated. For other oral drugs, NICE advise to "review the continued need" with insulin. We suggest:

- Sulfonylureas – usually stop.
- DPP4i (gliptins) – usually stop.
- Pioglitazone – usually stop (sometimes combine with insulin if very insulin resistant).
- SGLT2i – stop if patient is losing weight, slim, ketotic or for any other reason suspected to have type 1 diabetes or insulin deficiency. Continue if heart failure, arterial disease or high cardiovascular risk. Consider continuing if significant obesity or suspected insulin resistance.

Recommended insulin choices:

- Once- or twice-daily NPH insulin remains the first choice (*Humulin I, Insulatard* or *Insuman Basal*).
- If HbA1c >75 mmol/mol, consider a pre-mixed biphasic insulin (e.g. *Humulin M3, Insuman Comb 25/50*), or separate NPH and short-acting insulin.
- Consider insulin detemir (*Levemir*) or glargine (e.g. *Lantus/Abasaglar/Semglee*) if:
    - insulin has to be administered by a carer or nurse and use of detemir or glargine would reduce from two to one injection per day;
    - hypoglycaemia is a problem with NPH insulin.

Please see our separate guideline for insulin in type 2 diabetes

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Some comments on SGLT-2 inhibitors…

The data for cardiovascular protection for these drugs are persuasive. However, we are not certain that NICE were fully aware of the implications of their recommendations.

Local analysis of 600,000 patients in the UK Clinical Practice Research Datalink showed that 93% of people with type 2 diabetes met criteria in NG28 for an SGLT2i: 33.6% "offer SGLT2i" due to existing CV disease, and 59.6% "consider SGLT2i" due to QRisk >10%.

NICE TA775 separately advises dapagliflozin as an option if eGFR<75 (!). Unfortunately, TA775 was released at about the same time as NG28 but gives contradictory advice.

These two guidelines (NG28 and TA775) together support prescription of an SGLT2i for very nearly 100% of people with type 2 diabetes, even if HbA1c is already at target.

We agree that these are useful drugs, but **we advise that "consider" should not be understood to mean "recommended" or "usually recommended".** Rather, addition of an SLGT2i when HbA1c is already at target can be considered, taking into account the patient's feelings about taking an extra drug for the purposes of risk reduction. This conversation could be very similar to a discussion about statins for cardiovascular risk reduction, regardless of baseline cholesterol levels.

At the time of writing, there are some differences between **canagliflozin**, **dapagliflozin** and **empagliflozin** in terms of eGFR thresholds and official licensing for heart failure and CKD. These change frequently and we are not attempting to summarise them here. We expect these three drugs to have similar benefits.

However, we **do not currently recommend ertugliflozin**, which has so far failed to show the cardiovascular benefits of the other three drugs.

Diabetes drugs in low GFR

All drugs have some contraindications. Remember to check the BNF. We cannot and aren't attempting to provide a detailed list of exclusions. However, **at the time of writing and with emphasis that these thresholds tend to change fairly frequently**:

Metformin

- Metformin – avoid if eGFR less than 30 ml/minute/1.73m^2.

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SGLT-2 inhibitors

- Canagliflozin – OK if eGFR ≥60 – if eGFR30-59, max dose is 100mg daily – if eGFR<30, do not initiate and max continued dose is 100mg.
- Dapagliflozin – OK if eGFR ≥45 – if eGFR<45, glucose-lowering efficacy is reduced and probably absent in severe renal impairment – if eGFR<15, do not initiate**.**
- Empagliflozin – OK if eGFR ≥60 – if eGFR 30-59, can use if T2DM and established cardiovascular disease when max dose is 10mg daily – if eGFR<30, do not use for treatment of type 2 diabetes – if eGFR<20, do not use for treatment of heart failure.

Sulfonylureas

- Gliclazide – no specific restriction, but generally "use with care" in mild to moderate renal impairment – we would note that the risk of hypoglycaemia is always likely to be higher with insulin than with sulfonylureas.

DPP-4 inhibitors

- Alogliptin – if eGFR 30-50, max dose is 12.5mg– if eGFR <30, max dose is 6.25mg.
- Sitagliptin – if eGFR 30-45, max dose if 50mg – if eGFR <30, max dose is 25mg.
- Linagliptin – no dose adjustment required in renal impairment

GLP-1 mimetics

- Semaglutide (injected and oral), dulaglutide, liraglutide – no dose reduction in mild, moderate or severe renal impairment – not recommended in "end-stage renal disease" which we interpret as GFR<15.

Thiazolidinediones

- Pioglitazone – no official requirement to reduce dose, though in practice issues such as fluid retention or bone health prevent use in severe impairment.

How many different drugs should I try?

If your patient has inadequate control on triple therapy, and is keen to avoid insulin, you may wish to try other combinations. Switching one drug to a GLP-1 mimetic is a specific option in NICE guidance – usually if BMI>35, see above for other criteria.

Otherwise, all non-insulin drugs seem to have a fairly similar HbA1c-lowering effect. We do not expect to convert poor control to good control just by switching drugs around, and this may simply prolong poor control. Insulin therapy is usually recommended.

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However, possible options include changing a DPP4i or sulfonylurea to an SGLT2i, – or trying pioglitazone if the patient appears to be insulin resistant. We have occasionally seen a "jackpot" effect with these drugs.

Quadruple therapy is rarely used, and only by patients who adamantly will not take insulin. Four-drug combinations aren't illogical, but you must explain to the patient that they are not licensed or NICE-approved, and they must accept a risk of unknown adverse effects.