Antihyperglycaemic agents for Type 2 diabetes

We would like to thank the North West London Diabetes Clinical Reference Group for permission to adapt their guidance for use in North Central London.

This guideline was approved by the North Central London Diabetes and Weight Management Network in August 2022 & Joint Formulary Committee in September 2022 (Version 2.0).
NICE guidance\(^1\) (NG28) was partially updated in 2022 to assess the cost-effectiveness of SGLT2i and GLP-1 mimetics for cardiovascular risk reduction.

Key updates reflected in this guideline:
- SGLT2i (in combination with metformin) should be offered to those with chronic heart failure or established atherosclerotic cardiovascular disease, and considered for those at high risk of CVD
  - Atherosclerotic cardiovascular disease 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 CVD is defined as adults with type 2 diabetes who have:
    - QRISK2 more than 10% in adults aged 40 and over or
    - an elevated lifetime risk of cardiovascular disease (defined as the presence of 1 or more cardiovascular risk factors* in someone under 40)
      * hypertension, dyslipidaemia, smoking, obesity, and family history (in a first-degree relative) of premature CVD
- SGLT2i should be offered after establishing maximum tolerated ARB or an ACE inhibitor if ACR is $\geq 3$ mg/mmol for management of CKD
- GLP-1 mimetics are not cost-effective for CV risk reduction therefore can be used:
  - 3\(^{rd}\) line for those with:
    - BMI $\geq 35$ kg/m$^2$ ($\geq 30$ if BAME) \textit{and} psychological or medical problems associated with obesity
  - 4\(^{th}\) line for those with:
    - BMI $\geq 35$ kg/m$^2$ ($\geq 30$ if BAME) \textit{and} psychological or medical problems associated with obesity, \textit{or}
    - for whom insulin therapy would have significant occupational implications
Individualisation of HbA1c targets

Involves adults with type 2 diabetes in decisions about their individual HbA1c target. Encourage them to achieve the target and maintain it unless any resulting adverse effects (including hypoglycaemia), or their efforts to achieve their target, impair their quality of life. 

Offer lifestyle and dietary advice (NICE NG28, section 1.3) and drug treatment to support adults with type 2 diabetes to achieve and maintain their HbA1c target.

Approach to management of hyperglycaemia

- More stringent
- 53 mmol/mol
- Less stringent

Patient attitude and expected treatment efforts
- Highly motivated, adherent, Excellent self-care capacities
- Less motivated, non-adherent, Poor self-care capacities

Hypoglycaemia risk
- Low
- Moderate
- High

Disease duration
- 5
- 10
- 15
- 20

Life expectancy
- Long
- Short

Important comorbidities
- None
- Few/Mild
- Multiple/Severe

Established vascular complications
- Absent
- Severe

Resources, support system
- Readily available
- Limited
# Individualisation of HbA1c targets

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

- 3–6-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

Consider using [NICE patient decision add](#) to help set individualised HbA1c target, and consider potential distress if trying to achieve lower targets.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Target HbA1c presumption (this must be individualised)</th>
</tr>
</thead>
<tbody>
<tr>
<td>If <strong>any</strong> the following apply:</td>
<td></td>
</tr>
<tr>
<td>• Patients managed by lifestyle and diet alone, <em>or</em></td>
<td>48 mmol/mol (6.5%)</td>
</tr>
<tr>
<td>• Taking a single oral agent not associated with hypoglycaemia (metformin, gliptin, SGLT2-i, pioglitazone)</td>
<td></td>
</tr>
<tr>
<td>Two or more oral agents (or any agent associated with hypoglycaemia) and do not meet criteria for 58-64mmol/mol target.</td>
<td>53-57 mmol/mol (7.0-7.4%)</td>
</tr>
<tr>
<td>⬛ Intensify drug treatment if ≥ 58 mmol/mol (7.5%)</td>
<td></td>
</tr>
<tr>
<td>If older (e.g. age &gt; 60 years, or longer duration diabetes e.g. &gt; 10 years) and <strong>any</strong> the following apply:</td>
<td>58-64mmol/mol (7.5-8.5%)</td>
</tr>
<tr>
<td>• Tighter control will put them at higher risk if developed hypoglycaemia (e.g. risk of falling, impaired awareness of hypoglycaemia, people who drive or operate machinery as part of their job)</td>
<td></td>
</tr>
<tr>
<td>• Intensive management will not be appropriate due to significant comorbidities (including dialysis)</td>
<td></td>
</tr>
<tr>
<td>• Moderate frailty‡ (0.25-0.36 based on eFI score)</td>
<td></td>
</tr>
<tr>
<td>Patients who have severe frailty†‡ (&gt;0.36 based on eFI score) and/or not likely to achieve longer-term risk-reduction benefits e.g. reduced life expectancy</td>
<td>&lt; 75 mmol/mol (&lt; 9%)</td>
</tr>
</tbody>
</table>

† Either the ‘Rockwood Frailty Score’ or the ‘electronic Frailty Index’ (eFI), which is integrated into EMIS, can be used to guide the clinicians judgement of frailty. A holistic approach and awareness of multi-morbidity and polypharmacy should be taken when balancing the risk vs. benefit of diabetes treatment targets.†,20,21

‡ Avoid SU, caution insulin, avoid pioglitazone if HF and mindful renal function with metformin.
Management of type 2 diabetes in adults

**Diet & Lifestyle first line therapy**

High risk of CVD, chronic heart failure, established atherosclerotic CVD, or CKD with ACR ≥3?

**NO**

Rescue therapy: Insulin or SU

**Rescue based therapy** if symptomatic or high HbA1c

Review once symptoms resolved +/- target HbA1c achieved

**YES**

High risk of CVD
Age ≥40 & QRISK2 ≥10%, or Age <40 & ≥1 CV risk factors (see footer)

Chronic heart failure or established atherosclerotic CVD

CKD
ACR ≥3mg/mol & eGFR 25-75

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**Intensive diet & lifestyle management for all patients**

Consider enrolment into NCL Low-Calorie Diet Programme for eligible patients, to support healthier lifestyle, weight loss, and remission of Type 2 diabetes.

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**Metformin**

If intolerant, consider trial of modified release before moving to next level

**+ Sitagliptin**, or **Gliclazide, or Pioglitazone**, or **SGLT-2i**

Metformin

If intolerant, consider trial of modified release before moving to next level

When metformin tolerability confirmed, consider

+ **SGLT-2i**

As first line dual therapy, or second line to achieve HbA1c target.

Dapagliflozin strongest primary prevention data (HF)

**Metformin**

If intolerant, consider trial of modified release

When metformin tolerability confirmed

+ **SGLT-2i**

**eCVD**: Empagliflozin & Canagliflozin have shown benefit

HF: Dapagliflozin & Empagliflozin strongest data

**Metformin**

If intolerant, consider trial of modified release

When metformin tolerability confirmed, AND

Maximum tolerated ARB or ACEi + **SGLT-2i**

If not at glycaemic target, and eGFR <45mL/min, additional antihyperglycaemic agent will be required

**CKD**: Dapagliflozin & Canagliflozin strongest data

**If meets NICE criteria for use:**

+ **GLP-1 mimetic** (and stop any 'gliptin') if offered diabetes education programme (or EPP) and weight management programme (low calorie or dietician led) and has BMI ≥ 35 kg/m² (≥ 30 if BAME) + psychological or medical problems associated with obesity + HbA1c remain above target.

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**+ Basal insulin**

If meets criteria for use:

**+ GLP-1 mimetic** (and stop any 'gliptin')

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**CV risk factors**

Hypertension, dyslipidaemia, smoking, obesity, and family history (in a first-degree relative) of premature cardiovascular disease

**Rescue therapy: Insulin or SU**

Rescue based therapy if symptomatic or high HbA1c. Review once symptoms resolved +/- target HbA1c achieved

**When initiating a SGLT2i**

If HbA1c <58mmol/mol, consider a 25% dose reduction in any concomitant SU or basal insulin & monitor for evidence of hypoglycaemia

**When initiating a GLP-1RA or insulin**

Contact your Community Diabetes Service if you are not experienced with these medicines

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To avoid clinical inertia, reassess and modify treatment regularly (3-6 months)
# Dose adjustment in renal/hepatic impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>CKD stage 1 eGFR &gt;90 mL/min</th>
<th>CKD stage 2 eGFR 60-90 mL/min</th>
<th>CKD stage 3a eGFR 45-59 mL/min</th>
<th>CKD stage 3b eGFR 30-44 mL/min</th>
<th>CKD stage 4 eGFR 15-29 mL/min</th>
<th>CKD stage 5 eGFR &lt;15 mL/min</th>
<th>Mild to moderate hepatic impairment</th>
<th>Severe hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>Specialist initiation only</td>
<td>✗</td>
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<tr>
<td>Gliclazide</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Use lowest effective dose</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>100 mg</td>
<td>100 mg</td>
<td>100mg</td>
<td>50mg</td>
<td>25mg</td>
<td>25mg</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>10mg</td>
<td>10mg</td>
<td>10mg</td>
<td>10mg</td>
<td></td>
<td>Continue 10mg</td>
<td>✗</td>
<td>✗</td>
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<tr>
<td>Canagliflozin</td>
<td>Start 100mg, max 300mg</td>
<td>Start 100mg, max 300mg</td>
<td>100mg</td>
<td></td>
<td></td>
<td></td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>Start 10mg, max 25mg</td>
<td>Start 10mg, max 25mg</td>
<td>T2DM with eCVD: 10mg</td>
<td>T2DM with eCVD: 10mg</td>
<td>T2DM with HF and eGFR &lt; 20: ✗</td>
<td>T2DM with HF and eGFR ≥ 20: 10mg</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Ertugliflozin</td>
<td>Start 5mg, max 15mg</td>
<td>Start 5mg, max 15mg</td>
<td>Start 5mg, max 15mg</td>
<td></td>
<td></td>
<td></td>
<td>continue 5-15mg</td>
<td>✗</td>
</tr>
<tr>
<td>Semaglutide (SC)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>Caution: limited information</td>
<td>✗</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Semaglutide (oral)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>Caution: limited information</td>
<td>✗</td>
</tr>
<tr>
<td>Insulin</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>✗</td>
<td>✗</td>
</tr>
</tbody>
</table>

**Key**
- ✓ Initiate
- ✗ No new initiation; continue at stated dose
- ✗ Discontinue

*Caution: limited information*

**Be aware:** Diminished glycaemic effect of SGLT-2i with eGFR < 45 mL/min, however sustained cardio-renal protection; an additional glucose lowering agent may be required.
Additional guidance – SGLT2i

Cautions & contraindications

**Contraindications to SGLT2-i initiation by non-specialist** (if in doubt please refer to Diabetes Team):
- Type 1 Diabetes or Latent Autoimmune Diabetes of Adult (LADA)
- Patients previously presenting with DKA
- Ketosis-prone diabetes (including patients with pancreatic cancer/pancreatitis and patients who rapidly progressed to insulin treatment within 1 year of diagnosis)
- Very low carbohydrate or ketogenic diet ([link](#)), Eating Disorder or Very Low Calorie Diet
- Current acute illness (COVID-19, sepsis, vomiting, starvation for elective procedures)
- Acute diabetic foot ulceration / acute foot ischaemia
- Pregnancy/breast-feeding or female of child-bearing age not using contraception

**Cautions for initiation:**
- Diabetes with BMI < 25 kg/m² (consider possibility of type 1 DM)
- Frailty/cognitive impairment (increased risk of dehydration or hypotension)
- Diabetes with HbA1c >86 mmol/mol (10% DCCT) as increased risk of dehydration due to osmotic symptoms (control glycaemia with another agent THEN consider SGLT2-i)

Counselling points

ABCD have produced an educational resource for non-specialists to support safe initiation: [https://abcd.care/resource/s堡垒-2-inhibitors-type-2-diabetes-resource-HCPs-who-are-not-specialists](https://abcd.care/resource/s堡垒-2-inhibitors-type-2-diabetes-resource-HCPs-who-are-not-specialists)

**Signs and symptoms of DKA**
- Excessive thirst
- Polyuria
- Dehydration
- Shortness of breath and laboured breathing
- Abdominal pain
- Leg cramps
- Nausea and vomiting
- Mental confusion and drowsiness
- Ketones can be detected on the person’s breath (pear-drop smell) or in the blood or urine
**Definitions**

Established atherosclerotic CVD:
- Coronary heart disease
- Acute coronary syndrome,
- Previous myocardial infarction,
- Stable angina
- Previous coronary or other revascularisation
- Cerebrovascular disease (ischaemic stroke and transient ischaemic attack) Peripheral arterial disease

High risk of CVD in adults with type 2 diabetes:
- QRISK2 more than 10% in adults aged 40 and over or
- an elevated lifetime risk of cardiovascular disease (defined as the presence of 1 or more cardiovascular risk factors in someone under 40).

*Cardiovascular disease risk factors: hypertension, dyslipidaemia, smoking, obesity, and family history (in a first-degree relative) of premature cardiovascular disease.*
Additional guidance

**Sick Day Guidance** – to be reiterated to patients at every opportunity

When unwell (acute illness):

- Fever, sweats, shaking
- Vomiting / diarrhoea
- Unable to eat or drink

**Miss out / Omit / Pause:**

- S – SGLT-2i
- A – ACEi
- D – Diuretics
- M – Metformin
- A – ARBs
- N - NSAIDs

**After 2-3 days:**

- Feeling better = Restart paused medicines
- Not better = seek medical attention

Increase blood glucose monitoring during acute illness and check for ketones. If you are using daily insulin or an SUs, you may need to increase (or decrease) the amount taken to maintain appropriate glucose control. Ensure fluid intake to minimise dehydration.

**Lifestyle Counselling** – to be reiterated to patients at every opportunity

**Dietary Guidance**

Seek dietitian input. Individualised approach: low fat diet, low Glycaemic Index diet or Mediterranean diet etc. Alternatives include low calorie total diet replacement programmes (NCL Low-Calorie Diet Programme).

**Physical Activity**

Realistic targets should be set. The benefits of regular exercise should be explained and people should be advised to perform regular aerobic activity. Clinical studies show that walking for 30 minutes every day has cardiovascular benefits.

**Weight Management**

Weight loss can help the patient achieve Type 2 diabetes remission. Realistic initial weight loss target of 5% to 10% of starting weight. Consider drug therapy, e.g SLGT-2i or GLP-1. Consider surgical intervention.

**Smoking Cessation & Alcohol consumption**

Assess patients for smoking status and refer to Smoking Cessation Teams for support. Alcohol may influence blood glucose control (Hyper/Hypo glycaemia respectively).

**Medication review**

Reassess the person’s needs and circumstances at each review (3-6 months) and think about whether to stop any medicines that are not effective. Adjustments for Renal & Hepatic Impairment – see page 4.

**GLP-1RA**

Only continue in those with a beneficial metabolic response after 6 months (reduction of ≥11 mmol/mol [1.0%] in HbA1c and weight loss of ≥ 3% of initial body weight).

**SGLT-2i**

Stop & reassess if complicated by active foot ulcer or DKA (could be euglycemic).

**DPP-4i**

Not to be used in conjunction with GLP-1RA.

** TZD**

Stop in the event of HF, DKA or bladder cancer.

**SU**

In the event of significant hypos, stop & reassess.

**Diabetes Remission Programme**

Diabetes remission is a practical target for primary care. Consider enrolment into NCL Low-Calorie Diet Programme for Type 2 Diabetes for low calorie total diet replacement 3. For more details, click here.

Adapted from Imperial College Healthcare NHS Trust Renal Sick Day Rules
Lifestyle management should be part of the ongoing discussion with individuals with T2DM at each visit. Increasing physical activity and reducing body weight improves glycaemic control and should be encouraged in all people with T2DM. Glycaemic treatment targets should be individualised based on patient preferences and patient characteristics, including frailty and comorbid conditions. All drugs can cause side effects, consult BNF or summary of product characteristics for full side effect profile of individual drugs. Always offer advice on sick day guidance for patients on Metformin and/or SGLT-2i. Stop SGLT-2is peri-operatively or if restricted food intake or dehydration. Patients on insulin treatment should always be advised never to stop or significantly reduce their insulin as part of the sick day response. SU & TZD both have low acquisition cost, this should be taken into consideration alongside increased risk of weight gain and hypoglycaemia risk (SU).

Abbreviations:

T2DM: type 2 diabetes mellitus; NWL REWIND: North West London Reducing Weight with Intensive Dietary support, eGFR, estimated glomerular filtration rate; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; DPP-4i, dipeptidyl peptidase 4 inhibitor (gliptin); SU, sulfonylurea; TZD, thiazolidinedione; BMI, body mass index; GLP-1RA, glucagon-like peptide-1 receptor agonist; +ive, positive; CVD, cardiovascular disease; eCVD, established cardiovascular disease; MI, myocardial infarction; Cana, canagliflozin; Dapa, dapagliflozin; Empa, empagliflozin; HF, heart failure; CKD, chronic kidney disease; HbA1c, haemoglobin A1C; BD, twice daily; ACEi, Angiotensin-converting enzyme inhibitors; ARB, Angiotensin II receptor blocker; NSAID, Non-steroidal anti-inflammatory drug; DKA, diabetic ketoacidosis; uACR, urine albumin creatinine ratio; HFpEF, Heart Failure with reduced Ejection Fraction

References:

2. DIRECT; Lancet 2018; 391: 541–51 https://doi.org/10.1016/S0140-6736(17)33102-1
3. NCL Low-Calorie Diet Programme for Type 2 Diabetes For more details, click here
4. When prescribing an SGLT-2i, consider risk of volume depletion, euglycemia DKA in insulin deficient cohorts and lower limb amputation (class warning, but only observed in Cana and Erulu). Caution in frail patients and always follow sick day rules.
6. Sitagliptin is the only DPP-4i on the NCL Joint Formulary
8. REWIND (Dulaglutide CVOT); Lancet 2019; 394: 121–30; DOI: https://doi.org/10.1016/S0140-6736(19)31149-3
9. Patients with established atherosclerotic cardiovascular disease having had an ischemic event (e.g myocardial infarction or stroke)
10. Offer Metformin + SGLT-2i (rather than stepwise) for patients with chronic heart failure or established atherosclerotic CVD. Consider Metformin + SGLT-2i (rather than stepwise) for patients at high risk of CVD.
13. Dapa has shown MACE benefit in a post MI analysis; DECLARE prior MI; Circulation. 2019 May 28;139(22):2516-2527; DOI: https://doi.org/10.1161/CIRCULATIONAHA.119.039996
16. DAPA HF; September 19, 2019; DOI: https://doi.org/10.1056/NEJMo31911303
20. Type 2 diabetes mellitus in older people: a brief statement of key principles of modern day management including the assessment of frailty
https://www.guidelines.co.uk/diabetes/type-2-diabetes-frailty-in-older-people/545600.article