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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).

Background & rationale for update

- NICE guidance[1] (NG28) was partially updated in 2022 to assess the cost-effectiveness of SGLT2i and GLP-1 mimetics for cardiovascular risk reduction.

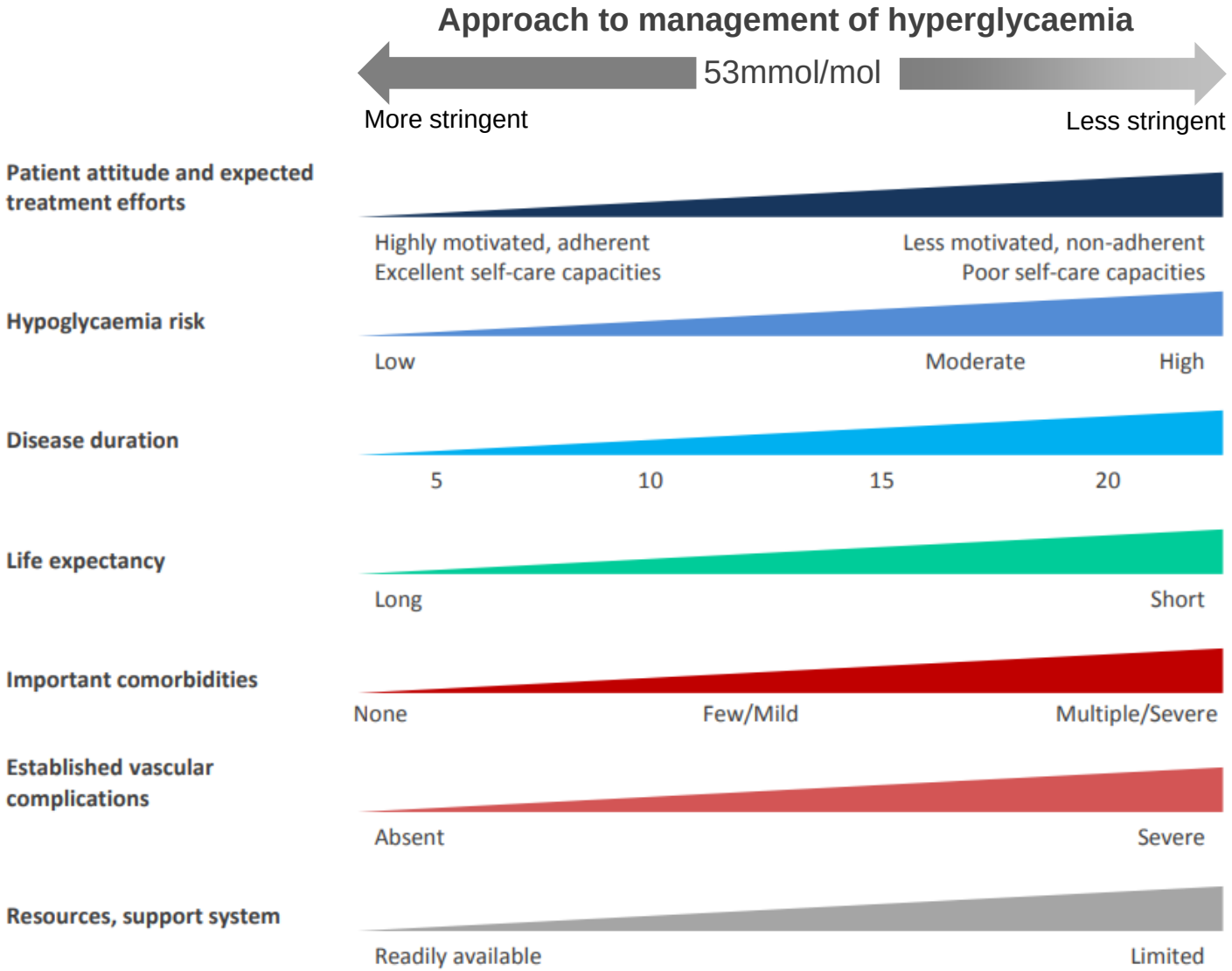
- Key updates reflected in this guideline:
  - SGLT2i (in combination with metformin) should be offered to those with chronic heart failure or established atherosclerotic cardiovascular disease, and considered for those at high risk of CVD
    - Atherosclerotic cardiovascular disease includes
      - 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 ≥3 mg/mmol for management of CKD
  - GLP-1 mimetics are not cost-effective for CV risk reduction therefore can be used:
    - 3rd line for those with:
      - BMI ≥ 35 kg/m^2 (≥ 30 if BAME) *and* psychological or medical problems associated with obesity
    - 4th line for those with:
      - BMI ≥ 35 kg/m^2 (≥ 30 if BAME) *and* psychological or medical problems associated with obesity, *or*
      - for whom insulin therapy would have significant occupational implications

Individualisation of HbA1c targets

Involve 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.[22]

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.



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.

Patient group	Target HbA1c presumption (this must be individualised)
If **any** the following apply: • Patients managed by lifestyle and diet alone, *or* • Taking a single oral agent not associated with hypoglycaemia (metformin, gliptin, SGLT2-i, pioglitazone)	48 mmol/mol (6.5%)
Two or more oral agents (or any agent associated with hypoglycaemia) and do not meet criteria for 58-64mmol/mol target.	53-57 mmol/mol (7.0-7.4%) *Intensify drug treatment if ≥ 58 mmol/mol (7.5%)*
If older (e.g. age > 60 years, or longer duration diabetes e.g. > 10 years) and **any** the following apply: • 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) • Intensive management will not be appropriate due to significant comorbidities (including dialysis) • Moderate frailty‡ (0.25-0.36 based on eFI score)	58-64mmol/mol (7.5-8.5%)
Patients who have severe frailty†,‡ (>0.36 based on eFI score) and/or not likely to achieve longer-term risk-reduction benefits e.g. reduced life expectancy	< 75 mmol/mol (< 9%)

† 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.[1,20,21]
‡ 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 [1,2,3]
Provide Sick Day Guidance (page 7)

To avoid clinical inertia, reassess and modify treatment regularly (3-6 months)

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

NO

Diet & Lifestyle first line therapy [2,3]
Metformin
If intolerant, consider trial of modified release before moving to next level

+ Sitagliptin[6], **or Gliclazide, or Pioglitazone**[7], **or SGLT-2i**[4]

YES

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

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

When metformin tolerability confirmed, consider
+ SGLT-2i [4, 10]
As first line dual therapy, or second line to achieve HbA1c target.

Dapagliflozin strongest primary prevention data (HF) [5]

Chronic heart failure or established atherosclerotic CVD

Metformin
If intolerant, consider trial of modified release

When metformin tolerability confirmed
+ SGLT-2i [4, 10]

eCVD: Empagliflozin & Canagliflozin have shown benefit
HF: Dapagliflozin & Empagliflozin strongest data [17, 18]

CKD
ACR ≥3mg/mol & eGFR 25-75

Metformin
If intolerant, consider trial of modified release

When metformin tolerability confirmed, AND
Maximum tolerated ARB or ACEi
+ SGLT-2i [4, 10]
If not at glycaemic target, and eGFR <45mL/min, additional antihyperglycaemic agent will be required

CKD: Dapagliflozin & Canagliflozin strongest data [16,19]

+ SGLT2i, or + Sitagliptin[6], **or Gliclazide, or Pioglitazone** avoid if heart failure[7], (or GLP-1 mimetic*)

*** Consider GLP-1 mimetic** (and stop any 'glipin') if offered diabetes education programme (or EPP) and weight management programme (low calorie or dietician led) **and** has BMI ≥ 35 kg/m^2 (≥ 30 if BAME) + psychological or medical problems associated with obesity + HbA1c remain above target.

+ Basal insulin

If meets NICE criteria for use :
+ GLP-1 mimetic
(and stop any 'gliptin')

Intensive diet & lifestyle management for all patients[1].

Consider enrolment into NCL Low-Calorie Diet Programme for eligible patients, to support healthier lifestyle, weight loss, and remission of Type 2 diabetes. [2,3]

Initial therapy

Treatment intensification to achieve individualised glycaemic target

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 HbA_{1c} Review once symptoms resolved +/- target HbA_{1c} achieved [1]
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

Dose adjustment in renal/hepatic impairment

Drug	**CKD stage 1** eGFR >90 mL/min	**CKD stage 2** eGFR 60-90 mL/min	**CKD stage 3a** eGFR 45-59 mL/min	**CKD stage 3b** eGFR 30-44 mL/min	**CKD stage 4** eGFR 15-29 mL/min	**CKD stage 5** eGFR <15 mL/min	**Mild to moderate hepatic impairment**	**Severe hepatic impairment**
Metformin	✓	✓	✓	✓ Max 500mg BD	✗	✗	Specialist initiation only	✗
Gliclazide	✓	✓	✓	✓	Use lowest effective dose	✗	✓	✗
Sitagliptin	✓ 100 mg	✓ 100 mg	✓ 100mg	✓ 50mg	✓ 25mg	✓ 25mg	✓	✗
Pioglitazone	✓	✓	✓	✓	✓	✓	✗	✗
Dapagliflozin	✓ 10mg	✓ 10mg	✓ 10mg	✓ 10mg	✓ 10mg	✓ Continue 10mg	✓	✓ Start 5mg, max 10mg
Canagliflozin	✓ Start 100mg, max 300mg	✓ Start 100mg, max 300mg	✓ 100mg	✓ 100mg	✓ Continue 100mg	✓ Continue 100mg	✓	✗
Empagliflozin	✓ Start 10mg, max 25mg	✓ Start 10mg, max 25mg	✓ T2DM with eCVD: 10mg	✓ T2DM with eCVD: 10mg	**T2DM only: ✗** **T2DM with HF and eGFR < 20: ✗** **T2DM with HF and eGFR ≥ 20:** 10mg	✗	✓	✗
Ertugliflozin	✓ Start 5mg, max 15mg	✓ Start 5mg, max 15mg	✓ Start 5mg, max 15mg	✓ Continue 5-15mg	✗	✗	✓	✗
Semaglutide (SC)	✓	✓	✓	✓	✓	✗	✓	Caution: limited information
Dulaglutide	✓	✓	✓	✓	✓	✗	✓	✓
Liraglutide	✓	✓	✓	✓	✓	✗	✓	✗
Semaglutide (oral)	✓	✓	✓	✓	✓	✗	✓	Caution: limited information
Insulin	✓	✓	✓	✓	✓	✓	✓	✓

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

Key

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

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/m^2 (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/sglt-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

Additional guidance – GLP-1RA

NICE eligibility criteria:

- **BMI ≥ 35 kg/m² (≥ 30 if BAME) *and* psychological or medical problems associated with obesity, or**
- **for whom insulin therapy would have significant occupational implications**

For those eligible for GLP-1 mimetic, treatment choice should be guided by treatment priority

	Weight loss as a secondary benefit of glucose lowering therapy	Primary CV risk reduction (if high risk of CVD)	Secondary CV risk reduction (if established atherosclerotic CVD)
Preferred	**Semaglutide subcutaneous** (once weekly) *28 days supply = 1 box of 1 pen, each pen contains four doses.*	**Dulaglutide** (once weekly) *28 days supply = 1 box of 4 pens, each pen contains one dose.*	**Semaglutide subcutaneous** (once weekly) *28 days supply = 1 box of 1 pen, each pen contains four doses.*
Alternative	**Semaglutide oral** (once daily) **Important notes:** • **Use subcutaneous semaglutide wherever possible**: greater efficacy and proven CV benefit • **Confirm person can adhere to the fasting administration requirement** (no tea, coffee, milk, food, other medicines for 30 minutes after dosing) **and an increase in total daily dosing frequency**		**Dulaglutide** (once weekly) *28 days supply = 1 box of 4 pens, each pen contains one dose.*

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.

Adapted from Imperial College Healthcare NHS Trust Renal Sick Day Rules

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 glycose 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).

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

DPP-4i
Not to be used in conjunction with GLP-1RA.

SU
In the event of significant hypos, stop & reassess.

Diabetes Remission Programme

Diabetes remission is a practical target for primary care[2]. Consider enrolment into **NCL Low-Calorie Diet Programme for Type 2 Diabetes** for low calorie total diet replacement [3].

For more details, click here

References and abbreviations

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[1]. Glycaemic treatment targets should be individualised based on patient preferences and patient characteristics, including frailty and comorbid conditions[1]. 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[1]. Stop SGLT-2is peri-operatively or if restricted food intake or dehydration[1]. Patients on insulin treatment should always be advised never to stop or significantly reduce their insulin as part of the sick day response[1]. 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; HbA_{1c}, 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; HFrEF, Heart Failure with reduced Ejection Fraction

References:

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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
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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)
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