ADA/EASD and NICE Recommendations on the Pharmacological Management of Type 2 Diabetes in Adults

Medscape UK X Guidelines
Primary Care Hacks

Authors: *Guidelines* editorial team, email: guidelines@webmd.net; Dr Kevin Fernando, GP Partner, North Berwick Health Centre; Content Advisor, Medscape Global and UK, email: kfernando@webmd.net

This Medscape UK Primary Care Hack highlights key recommendations from the American Diabetes Association/European Association for the Study of Diabetes and NICE on the management of hyperglycaemia in adults with T2D. As always, we should take an individualised and holistic approach to the care of people living with T2D.

ADA/EASD (2022)

INITIAL THERAPY

Implement comprehensive lifestyle measures for all people with T2D, including physical activity, weight reduction (including weight reduction medications), treatment adherence, nutrition, adequate sleep, and smoking cessation

DSMES should be offered on an ongoing basis, and be provided by trained diabetes care and education specialists

For treatment of hyperglycaemia, metformin remains the agent of choice in most people with diabetes

Other classes of agents are useful in combination with metformin or when metformin is contraindicated or not tolerated, with agent selection determined by the balance between the glucose-lowering efficacy and the side-effect profile of the individual agents[A]

Consider initial combination therapy with glucose-lowering agents, especially in those with high HbA_{1c} at diagnosis (i.e., >70 mmol/mol [>8.5%]), in younger people with T2D (regardless of HbA_{1c}), and in those in whom a stepwise approach would delay access to agents that provide cardio–renal protection beyond their glucose-lowering effects

Reinforce the importance of 24-hour physical behaviours (see Figure 2 in the full consensus statement):

- sitting/breaking up prolonged periods of sitting
- stepping
- sweating (moderate to vigorous exercise)
- strengthening
- sleep

FIRST INTENSIFICATION

All Patients	Established CVD and CV Risk Factors	HF	CKD	NAFLD/NASH
Combinations of agents are indicated in those who have HbA_{1c} levels >16.3 mmol/mol (>1.5%) above their target at diagnosis (e.g., ≥70 mmol/mol [8.5%] in most).[A] In particular, among young adults with T2D, immediate and sustained glycaemic management should be pursued, aiming for HbA_{1c} of 53 mmol/mol (7%) or lower In younger people with diabetes (<40 years), consider early combination therapy	In patients with established CVD, a GLP-1 RA with proven benefit should be used to reduce MACE, or an SGLT2i with proven benefit should be used to reduce MACE and HF and improve kidney outcomes[B],[C] In individuals without established CVD but with multiple CV risk factors (such as age ≥55 years, obesity, hypertension, smoking, dyslipidaemia, or albuminuria), a GLP-1 RA with proven benefit could be used to reduce MACE, or an SGLT2i with proven benefit could be used to reduce MACE and HF and improve kidney outcomes[B],[C]	In people with HF, SGLT2i should be used because they improve HF and kidney outcomes[B],[C]	In people with CKD and an eGFR ≥20 ml/min/1.73 m^2 and a UACR >3.0 mg/mmol (>30 mg/g), an SGLT2i with proven benefit should be initiated to reduce MACE and HF and improve kidney outcomes[B],[C] If treatment with an SGLT2i is not tolerated or is contraindicated in people with CKD and an eGFR ≥20 ml/min/1.73 m^2 and a UACR >3.0 mg/mmol (>30 mg/g), a GLP-1 RA with proven CV outcome benefit could be considered to reduce MACE and should be continued until kidney replacement therapy is indicated[B],[C] In general, selection of medications to improve CV and kidney outcomes should not differ for older people	For those with NAFLD/NASH at high risk of fibrosis, pioglitazone could be considered There is emerging evidence for benefits of metabolic surgery and three classes of glucose-lowering therapy (GLP-1 RA, SGLT2i, and GIP and GLP-1 RA)

SECOND INTENSIFICATION

In general, intensification of treatment beyond two medications follows the same general principles as the addition of a second medication, with the assumption that the effectiveness of third and fourth medications will be generally less than when they are used alone. While solid evidence exists for combining SGLT2i and GLP-1 RAs for weight and glucose lowering, emerging data also suggest promise for combined effects on cardio–renal outcomes

When glycemic measurements do not reach targets, and insulin is the best choice for the individual, its introduction should not be delayed[D],[E]

THIRD INTENSIFICATION

Metabolic surgery should be considered as a treatment option in adults with T2D who are appropriate surgical candidates with a BMI ≥40.0 kg/m^2 (BMI ≥37.5 kg/m^2 in people of Asian ancestry) or a BMI of 35.0–39.9 kg/m^2 (32.5–37.4 kg/m^2 in people of Asian ancestry) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycaemia) with nonsurgical methods

NICE (2022)

FIRST-LINE TREATMENT

Assess HbA_{1c}, CV risk, and kidney function[F]

Reinforce advice about diet, lifestyle, and adherence to drug treatment if HbA_{1c} levels are not adequately controlled by a single drug and rise to ≥58 mmol/mol (7.5%)

Not at High CVD Risk	CHF or Established ASCVD[H]	High Risk of CVD (QRISK2 ≥10%)
Offer standard-release metformin or if GI disturbance, metformin MR If metformin contraindicated consider: • DPP-4 inhibitor **or** • pioglitazone **or** • sulfonylurea • an SGLT2i for some people (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)[G]	Offer standard-release metformin or if GI disturbance, metformin MR And, as soon as metformin tolerability is confirmed,[I] **offer** SGLT2i with proven CV benefit If metformin contraindicated **offer** SGLT2i alone[G]	Offer standard-release metformin or if GI disturbance, metformin MR And, as soon as metformin tolerability is confirmed,[I] **consider** SGLT2i with proven CV benefit If metformin contraindicated **consider** SGLT2i alone[G]

TREATMENT OPTIONS IF FURTHER INTERVENTIONS ARE NEEDED[J]

At Any Point, if HbA_{1c} Not Controlled Below Individually Agreed Threshold	At Any Point, if the Person Has or Develops CHF or Established ASCVD[H]	At Any Point, if the Person Has a High Risk of CVD (QRISK2 ≥10%)
Switching or adding treatments: • DPP-4 inhibitor **or** • pioglitazone **or** • sulfonylurea • SGLT2i may also be an option in dual therapy or triple therapy	Switching or adding treatments: **offer** an SGLT2i (if not already prescribed)	Switching or adding treatments: **consider** an SGLT2i (if not already prescribed)

TREATMENT OPTIONS IF FURTHER INTERVENTIONS ARE NEEDED

Insulin Therapy

When dual therapy has not continued to control HbA_{1c} to below the person's individually agreed threshold, also consider insulin-based therapy (with or without other drugs):

- dapagliflozin, empagliflozin, canagliflozin

GLP-1 Mimetic Treatments

If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated, or contraindicated, consider triple therapy by switching one drug for a GLP-1 mimetic for adults with T2D who:

- have a BMI ≥35 kg/m^2 (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 <35 kg/m^2 **and**:
  - ◊ for whom insulin therapy would have significant occupational implications **or**
  - ◊ weight loss would benefit other significant obesity related comorbidities

Footnotes

[A] When targets are not met, in addition to addressing health behaviours and referral to DSMES, the intensification of glucose-lowering medication by combining agents with complementary mechanisms of action should be pursued. Traditionally, a stepwise approach was advocated, in which a new agent is added to the existing regimen, but evidence is growing to support a more proactive approach in many by combining glucose-lowering agents from initial diagnosis
[B] In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or an SGLT2i with proven benefit should be independent of background use of metformin
[C] In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or an SGLT2i with proven benefit should be independent of baseline HbA_{1c}. Agents that cause hypoglycaemia, such as sulfonylureas, should be discontinued once insulin is started
[D] The use of a GLP-1 RA should be considered prior to initiation of insulin
[E] When initiating insulin, start with a basal insulin and intensify the dose in a timely fashion, titrating to achieve an individualised fasting glycaemic target set for every person
[F] For information on using an SGLT2i for people with T2D and CKD see the section on diabetic kidney disease in the full guideline
[G] NICE technology appraisals recommend an SGLT2i as monotherapy options in people who cannot have metformin for whom diet and exercise alone do not provide adequate glycaemic control. An SGLT2i is recommended only if a DPP-4 inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate. In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines
[H] Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease
[I] Start metformin alone to assess tolerability before adding an SGLT2i
[J] At each point follow the prescribing guidance. Switch or add treatments from different drug classes up to triple therapy (dual therapy if metformin is contraindicated). In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines

Abbreviations

ASCVD=atherosclerotic cardiovascular disease; **BMI**=body mass index; **CHF**=chronic heart failure; **CKD**=chronic kidney disease; **CV**=cardiovascular; **CVD**=cardiovascular disease; **DPP-4**=dipeptidyl peptidase 4; **DSMES**=diabetes self-management education and support; **eGFR**=estimated glomerular filtration rate; **GI**=gastrointestinal; **GIP**=glucose-dependent insulinotropic polypeptide; **GLP-1 RA**=glucagon-like peptide-1 receptor agonists; **HbA_{1c}**=glycated haemoglobin A_{1c}; **HF**=heart failure; **MACE**=major adverse cardiovascular events; **MR**=modified release; **NAFLD**=non-alcoholic fatty liver disease; **NASH**=non-alcoholic steatohepatitis; **SGLT2i**=sodium–glucose cotransporter 2 inhibitor; **T2D**=type 2 diabetes; **QRISK**=cardiovascular risk score; **UACR**=urine albumin–creatinine ratio.

References

1. Davies M, Aroda V, Collins B et al. Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2022; **45** (11): 2753–2786. Available at: diabetesjournals.org/care/article/doi/10.2337/dci22-0034/147671/Management-of-Hyperglycemia-in-Type-2-Diabetes
2. NICE. *Type 2 Diabetes in Adults: Management*. NICE, 2015 (updated June 2022). Available at: nice.org.uk/guidance/ng28.