Diabetes: HbA_{1c}

1. Background information

- The UK Prospective Diabetes Study (UKPDS) Group demonstrated strong, long term evidence that intensive glycaemic control is strongly associated with significant clinical benefits for people with type 2 diabetes (T2D).[1]
- Every 1% decrease in HbA_{1c} is associated with clinically important reductions in the incidence of diabetes-related death (21%), myocardial infarction (14%), microvascular complications (37%), and amputation or death from peripheral vascular disease (43%).[2]
- Data from the UK Prospective Diabetes Study 10-year follow-up demonstrated that there are long-term benefits of early glycaemic control. This was true despite the difference in HbA_{1c} between the different treatment arms being lost one year after the 10-year post-trial follow up commenced (known as the "legacy effect").[3]

Guidelines

For the management of hyperglycaemia in adults with T2D, NICE guideline 28 recommends the following:[4]

- Reinforce advice on diet, lifestyle and adherence to drug treatment.
- Agree an individualised HbA_{1c} target based on: the person's needs and circumstances including preferences, co-morbidities, risks from polypharmacy and tight blood glucose control and ability to achieve longer-term risk-reduction benefits. Where appropriate, support the person to aim for the HbA_{1c} levels in the NICE algorithm.

  Measure HbA_{1c} at 3 to 6 monthly intervals, as appropriate. If the person achieves an HbA_{1c} target lower than target with no hypoglycaemia, encourage them to maintain it.
- Base the choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, the person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if two drugs in the same class are appropriate, choose the option with the lowest acquisition cost).

2. Targets

The HbA_{1c} targets proposed by NICE guideline 28 are as follows:[4]

Manage by lifestyle and diet +/- a single glucose-lowering agent not associated with hypoglycaemia.	Support person to aim for an HbA_{1c} level of 48 mmol/mol (6.5%).
Manage by lifestyle and diet +/- a single glucose-lowering agent associated with hypoglycaemia, e.g. a sulphonylurea.	Support person to aim for an HbA_{1c} level of 53 mmol/mol (7%).
If HbA_{1c} level rises to 58 mmol/mol (7.5%) or higher on more than one glucose-lowering agent: Reinforce advice about diet, liefstyle and adherence to drug treatment and support person to aim for an HbA_{1c} level of 53 mmol/mol (7.0%) and intensify drug treatment.	

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- An annual HbA_{1c} is one of the 9 key care processes within the National Diabetes Audit. There are two HbA_{1c} targets: ≤58 mmol/mol (7.5%) without frailty and ≤75 mmol/mol (9%) with moderate or severe frailty.[5] Avoiding a lower target for those with moderate or severe frailty reduces the risk of over-treating this group and focuses on achieving better control in those likely to gain the greatest benefit.
- It should be noted that the target indicator of 58 mmol/mol (7.5%) is higher than those presented in NICE guideline 28 (48 or 53 mmol/mol [6.5 or 7.0%]) but does represent the point at which treatment intensification should be considered in T2D.[4]

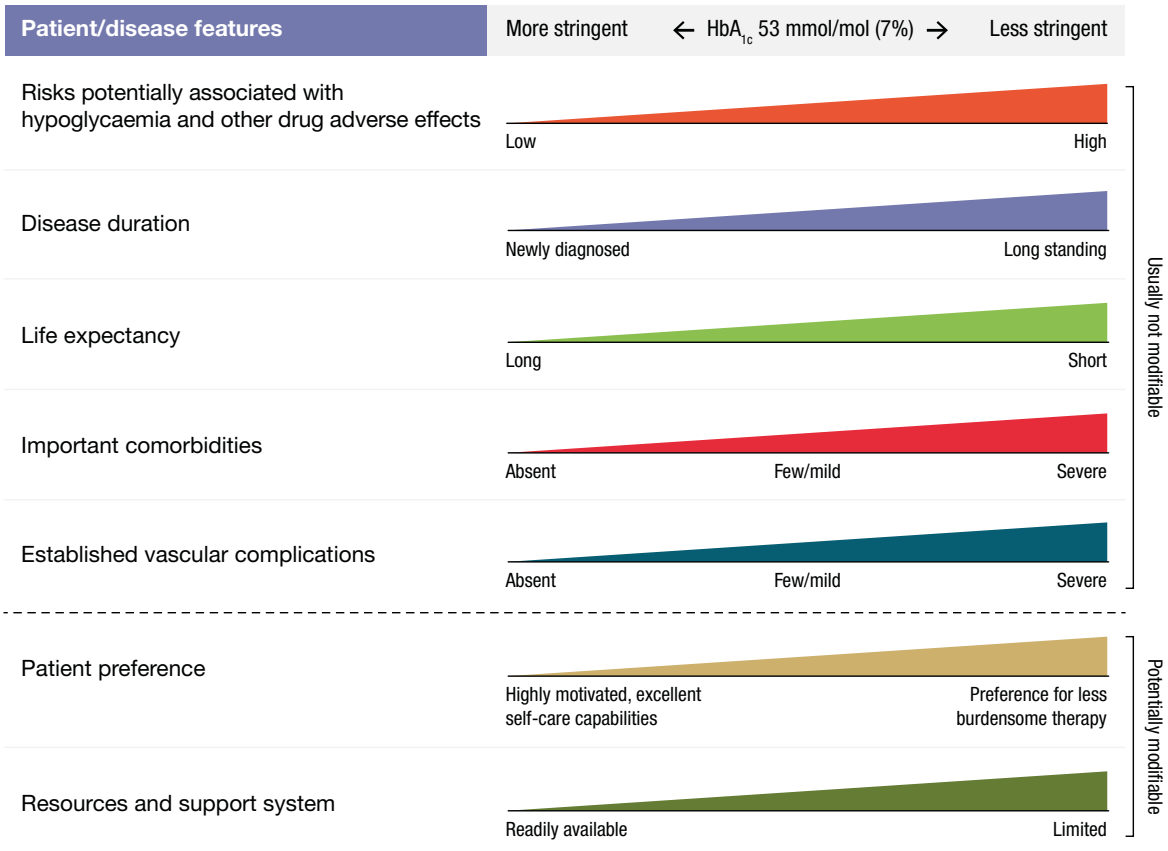
Individualisation

The individualised approach advocated is one tailored to the needs and circumstances of adults with type 2 diabetes. This should consider their personal preferences, co-morbidities, risks from polypharmacy, and their ability to benefit from long-term interventions:[4]

- Consider relaxing the target HbA_{1c} level on a case-by-case basis. Think about the older and frail who are unlikely to achieve longer-term risk-reduction benefits. And consider those for whom tight blood glucose control poses a high risk of the consequences of hypoglycaemia, including: those at risk of falling, people who have impaired awareness of hypoglycaemia, or individuals who drive or operate machinery as part of their work.[4]

The diagram below initially developed for the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) consensus report helps to explain the personalised approach to the management of hyperglycaemia.[6]

Approach to individualisation of glycaemic targets



3. Management

Clinical trials on the cardiovascular safety of medications for T2D have led to a paradigm shift in glucose-lowering treatment. Two groups of diabetes drugs – glucagon-like peptide-1 receptor agonists (GLP-1 RA) and sodium-glucose cotransporter-2 (SGLT-2) inhibitors – have showed cardiovascular benefit in patients with diabetes or those with existing heart disease and/or multiple risk factors.

NICE guideline 28 does not reflect the latest cardiovascular outcome trial (CVOT) evidence and many clinicians now refer to the more recently published ADA/EASD consensus report.[7] It advocates preferential consideration of agents demonstrating cardiovascular (CV) benefit in those with established cardiovascular disease (CVD) or chronic kidney disease (CKD). This step-wise approach is illustrated on the next page.

4. Choice of therapy

- ☐ Reassess the person's needs and circumstances at each review and think about whether to stop ineffective medicines.[4]
- ☐ Discuss the benefits and risks of drug treatment and the options available with the patient.[4]
- ☐ Follow the latest guidance on therapy options.[7]

5. Ongoing Monitoring

NICE guideline 28 recommends checking HbA_{1c} levels at:[4]

- ☐ 3 to 6-monthly intervals (tailored to individual needs), until the HbA_{1c} is stable on unchanging therapy.
- ☐ 6-monthly intervals once the HbA_{1c} level and blood glucose-lowering therapy are stable.
- ☐ Involve adults with T2D in decisions about their individual HbA_{1c} target.
- ☐ Encourage them to achieve the target and maintain it unless there are any adverse effects (including hypoglycaemia), or their efforts to achieve the target impairs their quality of life.
- ☐ Consider the person's individual preferences and needs.

6. Useful resources

- **Diabetes UK: Diabetes and high HbA_{1c}: Information prescription**
  https://www.diabetes.org.uk/resources-s3/2018-02/Diabetes%20UK%20Information%20Prescription_HbA1c.pdf

References

1. UK Prospective Diabetes Study (UKPDS) Group (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–53. **2.** Stratton IM et al (2000) Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321:405–12. **3.** Holman RR et al (2008) 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 359:1577–89. **4.** National Institute for Health and Care Excellence (2015) *Type 2 Diabetes in Adults: Management.* Available at: https://www.nice.org.uk/guidance/ng28 [Accessed February 2020]. **5.** National Institute for Health and Care Excellence (2018) *New indicators added to the NICE indicator menu for general practice.* Available at: https://www.nice.org.uk/Media/Default/Standards-and-indicators/indicators-general-practice.pdf [Accessed February 2020]. **6.** American Diabetes Association (2020) Glycemic targets: Standards of medical care in diabetes. *Diabetes Care* 43(S1): S66–S76. **7.** Buse JB et al (2020) 2019 Update to: Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 43:487–97.

First-line therapy is metformin and comprehensive lifestyle interventions*
(Including weight management and physical activity). If HbA_{1c} above target proceed as below:

With established ASCVD or CKD or HF

ASCVD predominates

Preferably	Or
GLP-1 RA with proven CVD benefits[1]	SGLT-2i with proven CVD benefit if eGFR adequate[2]

If HbA_{1c} above target

If further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT-2i, choose agents demonstrating CV safety:

- For patients on a GLP-1 RA, consider adding SGLT-2i with proven CVD benefit[1]
- DPP-4i if not on GLP-1 RA
- Basal insulin[5]
- TZD[6]
- SU[7]

HF or CKD predominates

Preferably	Or
SGLT-2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]	If SGLT-2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1RA with proven CV benefit[1,4]

If HbA_{1c} above target

- Avoid TZD in the setting of HF

Choose agents demonstrating CV safety:

- For patients on a SGLT-2i, consider adding GLP-1 RA with proven CVD benefit[1]
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin[5]
- SU[7]

Without established ASCVD or CKD

Compelling need to minimise hypoglycaemia

GLP-1 RA Or DPP-4i
Or Or
TZD Or SGLT-2i[2]

Compelling need to minimise weight gain or promote weight loss

GLP-1 RA with good efficacy for weight loss[8]
Or
SGLT-2i[2]

Cost is a major issue

SU[6]
Or
TZD

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

Full supporting details for these two algorithms are provided in reference 7 (Buse et al 2020)
ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; SU, sulphonylurea; TZD, thiazolidinedione.

- **In the UK, SGLT-2is can only be initiated if the eGFR is ≥60 mL/min/1.73 m². For other medicines please consult the respective SmPC for renal prescribing guidance.**
- **All products referenced are licensed for insufficiently controlled T2D or improvement of glycaemic control in T2D.**

1. Proven CVD benefit means it has label indication of reducing CVD events. **2.** Be aware that SGLT-2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use. **3.** Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE, dapagliflozin has primary heart failure outcome data from DAPA-HF. **4.** Caution with GLP-1 RAs in ESRD. **5.** Degludec and U100 glargine have demonstrated CVD safety. **6.** Low dose may be better tolerated though less well-studied for CVD effects. **7.** Choose later generation SU to lower risk of hypoglycaemia; glimepiride has shown similar CV safety to DPP-4i. **8.** Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide.

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