Tablet Press Extra
The prescribing newsletter for GPs, nurses and pharmacists
NHS Northamptonshire CCG
March 2021

New treatment guidance for type 2 diabetes management

Background
Since 2008, following the withdrawal of rosiglitazone amid concerns about cardiovascular safety, the regulatory bodies in the US and Europe have mandated cardiovascular outcome trials (CVOTs) on all new glucose lowering medications to demonstrate safety.

The agreed primary outcome measure is known as 3-point MACE (Major Adverse Cardiovascular Events) defined as cardiovascular death; non-fatal myocardial infarction and non-fatal stroke. Some studies had secondary outcomes such as hospitalisation for congestive heart failure and progression of renal disease.

Result of CVOTs and international guideline changes

- No CVOT has revealed any cardiovascular safety concerns for GLP-1 receptor analogues or SGLT-2 inhibitors. Most DPP-4 inhibitors have shown non-inferiority for CV events but saxagliptin was associated with increased risk of hospitalisation for heart failure and should not be used in the presence of heart failure.
- Some agents in the SGLT-2i and GLP-1RA classes have demonstrated cardiovascular and/or renal benefit.
- In 2018 the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) produced a consensus guideline for treatment of type 2 diabetes[1], with minor revision in 2019[2].
- In the UK, NICE is working on a major update to the 2015 guideline (last minor update in August 2019[3]) but no publication date for the revision has been confirmed.
- Since the current NICE guidance does not reflect the latest CVOT data, which demonstrates clear evidence of patient benefit for certain drugs, it was agreed that producing some Northamptonshire guidance would be helpful for clinicians and beneficial for their patients.

Local guideline development
Representatives of diabetes teams in Kettering, Northampton and the community have worked with the cardiovascular lead and the medicines management lead at Northamptonshire CCG to agree a local guideline, with the following aims:

- Identify those at increased risk of cardiovascular events and recommend blood glucose lowering therapy which has potential to reduce CV risk
- Reduce use of treatments which do not have potential for CV benefit
- Identify those at increased risk of hypoglycaemia and avoid use of hypoglycaemia inducing treatments
- Identify people where weight is a significant issue and select treatments which are likely to help with weight loss.

The local guideline closely follows the ADA/EASD recommendations and has used best currently available evidence to advise on choice of agent, bearing in mind that trials are not directly comparable and that new evidence may emerge in the future. Link

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Summary of guidance for management of type 2 diabetes

Along with lifestyle and dietary advice, metformin remains first line treatment. Further decisions depend on the following criteria:

1. Is the person at high risk of a cardiovascular event* OR is there a history of renal disease?**

* Previous cardiovascular event OR age >55years + LVH or >50% stenosis of coronary, carotid or lower extremity artery
**eGFR 30-60 or urinary albumin:creatinine ratio >30mg/mmol

If YES, consider adding:

- SGLT-2 inhibitor with proven cardiovascular benefit
  Link to Choice of SGLT-2i (See slide 3)
- If SGLT-2i unsuitable or not tolerated consider a GLP-1 RA with proven cardiovascular benefit
  Link to Choice of GLP-1RA (See slide 4)

2. If CV risk is not high and treatment escalation is required, consider whether either of the following applies:

a. Compelling need to avoid hypoglycaemia:

- Avoid sulfonylurea (SU) and insulin and seek specialist advice if one of these options considered unavoidable
- Choose from SGLT-2i; DPP-4i; GLP-1RA; thiazolidinedione (TZD). **See further considerations below, appendix 1 (choosing the best option for the individual) and**
  Link to medication algorithm (See slide 2)

b. Compelling need to avoid weight gain:

- Select agents with potential to promote weight loss:
  SGLT-2i (preferred)
  Link to Choice of SGLT-2i (See slide 3)
- GLP-1RA if SGLT-2i unsuitable or not tolerated
  Link to Choice of GLP-1RA (See slide 4). Avoid agents promoting weight gain (SU, TZD, insulin) unless there is no alternative

Further considerations

1. Sick day rules
   In certain circumstances some agents should be stopped during intercurrent illness. Sick day rules can be accessed here Link to Sick Day Rules (See slide 9)

2. Agreeing an individualised HbA1c target
   This needs to take into account the benefits and potential adverse effects of the HbA1c target:
   Link to HbA_{1c} individualised target slides (See slide 7)

3. SGLT-2i can be introduced irrespective of HbA1c if indicated on grounds of CV benefit. SGLT-2i do not cause hypoglycaemia UNLESS added to hypoglycaemia inducing agent (eg SU or insulin). If HbA1c at or close to target, reduce dose or stop SU/insulin when SGLT-2i is introduced.

4. Select SGLT-2i in preference to DPP-4i unless contraindicated or not tolerated - greater cardiovascular and renal benefit. If person is already taking a DPP-4i but is suitable for SGLT-2i, stop DPP-4i and commence SGLT-2i.

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5. For frail older people a DPP-4i is the agent of choice if SGLT-2i unsuitable.
   Avoid the following where possible and use recommended treatment targets and de-escalation threshold: Link to HbA1c individualised targets (See slide 7)
   - SU and insulin (risk of hypoglycaemia)
   - TZD (risk of heart failure and fracture)
   - GLP-1RA (need to avoid appetite suppression in most frail people)

6. Renal impairment
   Select an SGLT-2i with proven renal benefit
   Link to Choice of SGLT-2i (slide 3)
   If SGLT-2i contraindicated or not tolerated, ensure that the alternative agent selected is suitable for the person's eGFR and monitor renal function

7. Active foot disease or at risk of amputation
   Avoid initiating SGLT-2i unless on recommendation of specialist foot team. Refer new onset foot disease to specialist foot team urgently.

8. Semaglutide: once weekly injectable (Ozempic) or daily oral (Rybelsus)
   - **Ozempic is more effective in terms of glucose lowering and weight loss and has proven cardiovascular benefit. It should be used in preference to Rybelsus unless there is a strong reason for not taking an injection.**
   - Rybelsus has variable absorption and CV benefit is not yet proven. It **MUST** be taken first thing in the morning on an empty stomach with only a small amount of water. This may impact on adherence.

9. GLP-1RA and retinopathy monitoring
   - There is some evidence to suggest that some people with pre-existing retinopathy may experience deterioration in their retinopathy after starting a GLP-1RA.
   - This *may* be related to the fall in HbA1c. (This may also be seen when HbA1c falls following insulin initiation.)
   - In view of the current uncertainty, monitoring of retinopathy is recommended for people with existing retinopathy who commence a GLP-1RA. The local monitoring pathway can be found here Link to retinopathy slide (See slide 6)

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References

Type 2 diabetes treatment guidelines

1. ADA/EASD guideline 2018 https://care.diabetesjournals.org/content/41/12/2669
2. ADA/EASD update 2019 https://care.diabetesjournals.org/content/early/2019/12/18/dci19-0066
3. NICE 2015 (minor update 2019) https://www.nice.org.uk/guidance/ng28

Cardiovascular outcome trials:
Trial outcomes are not directly comparable because of differences in participant cohorts

SGLT-2 inhibitors

4. EMPA-REG https://www.nejm.org/doi/full/10.1056/nejmoa1504720
5. DECLARE-TIMI 58 https://www.nejm.org/doi/full/10.1056/NEJMoa1812389
6. CREDENCE https://www.nejm.org/doi/full/10.1056/nejmoa1811744
8. DAPA-HF https://www.nejm.org/doi/full/10.1056/NEJMoa1911303

GLP-1RAs

9. LEADER https://www.nejm.org/doi/full/10.1056/NEJMoa1603827
10. SUSTAIN 6 https://www.nejm.org/doi/full/10.1056/nejmoa1607141
11. REWIND Lancet. 2019 Jul 13;394(10193):121-130.
12. SUSTAIN 7 https://www.thelancet.com/journals/landia/article/PIIS2213-8587(18)30024-X/fulltext
13. AWARD-11 https://diabetes.diabetesjournals.org/content/69/Supplement_1/357-OR
14. PIONEER 6 https://www.nejm.org/doi/full/10.1056/NEJMoa1901118

GLP-1RA retinopathy data from CVOTs
Trial outcomes are not directly comparable because of differences in prevalence/severity of retinopathy at baseline and in reduction in HbA1c.

15. SUSTAIN 6 (semaglutide) https://www.nejm.org/doi/full/10.1056/nejmoa1607141
16. REWIND (dulaglutide) https://doi.org/10.1016/S0140-6736(19)31149-3
17. LEADER (liraglutide) https://www.nejm.org/doi/full/10.1056/NEJMoa1603827
18. SUSTAIN 6 (post hoc analysis) https://dom-pubs.onlinelibrary.wiley.com/doi/full/10.1111/dom.13172
19. A detailed analysis of the retinopathy data can be requested from Dr Pierides

Individualised HbA1c targets

20. UKPDS Group* 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 1998;352:837-853. doi:https://doi.org/10.1016/S0140-6736(98)07019-6
21. Holman et al. 10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes. https://www.nejm.org/doi/full/10.1056/nejmoa0806470

Frailty treatment and de-escalation treatment targets

22. Strain et al 2018 https://doi.org/10.1111/dme.13644

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APPENDIX 1

Choosing the best option for the individual: consider positives and negatives below and select best option for the individual, taking into account individual treatment target*

Agents for use when compelling need to avoid hypoglycaemia

SGLT-2i

Positives

- HbA1c reduction 8mmol/mol
- No hypoglycaemia
- Promotes weight loss
- CV benefit for high risk groups
- Renal protection for CKD 3-5 and proteinuria (initiate if eGFR >30)

Negatives

- Urogenital infection risk
- Avoid in frailty*
- Small risk of DKA
- Stop during intercurrent illness
- Avoid in active foot disease unless on specialist advice

DPP-4i:

Positives

- HbA1c reduction 7-8mmol/mol
- No hypoglycaemia
- Weight neutral
- Suitable for people with frailty in whom HbA1ic is above frailty-adjusted individual target target*

Negatives

- No CV benefit
- Modest HbA1c reduction with no additional benefit

TZD (pioglitazone):

Positives

- HbA1c reduction 11-22mmol/mol
- No hypoglycaemia
- Reduces insulin resistance

Negatives

- Weight gain
- Fluid retention
- Contraindicated ii risk of heart failure
- Risk of fracture
- Avoid if past or current bladder cancer and check for haematuria before commencing
- Avoid in liver impairment and monitor liver function
- Avoid in frailty

GLP-1RA:

Positives

- HbA1c reduction 9-17mmol/mol
- No hypoglycaemia
- Weight loss
- CV benefit (liraglutide, semaglutide (injectable only) and dulaglutide)

Negatives

- GI side effects
- Avoid in active gall bladder disease
- Possible risk of pancreatitis in trials not confirmed following widespread use
- Small risk of deterioration of existing retinopathy
- Usually unsuitable in frailty

Additional treatment options - seek specialist advice if compelling need to avoid hypoglycaemia or weight gain

Sulphonylurea:

Positives

- HbA1c reduction 22mmol/mol
- Rapid clinical response - can be useful if BG high

Negatives

- Hypoglycaemia - avoid in older people because of hypo-induced risk of falls/arrhythmias/stroke and increased risk of hospital admission for treatment of hypos
- BG monitoring essential
- Weight gain
- No CV benefit

Insulin:

Positives

- Effective BG reduction provided carbohydrate intake controlled
- Required for people with reduced insulin production (eg normal/low body weight)
- Absence of other side effects

Negatives

- Hypoglycaemia
- BG monitoring essential
- Weight gain
- No CV benefit

***HbA1c targets in people with frailty**

Frailty assessment	Treatment target HbA1c mmol/mol	De-escalation threshold HbA1c mmol/mol
Fit older adult	58	53
Moderate to severe	64	58
Very severe	70	64

Strain et al 2018 https://doi.org/10.1111/dme.13644

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