Suffolk and North East Essex Integrated Care Board (ICB)

Local NHS Integrated Care Board (ICB) guideline for pharmacological management of Type-2 Diabetes

Rationale for this guideline:

This guideline is our local ICB response to the NICE NG28 guideline which was published by NICE UK on 15th February 2022 [1]. It summarises our local modification of this guideline across the ICS. This version has been modified to include Tirzepatide (Mounjaro®) as per NICE TA924

Key stakeholders:

1. Senior members of the diabetes team at Ipswich Hospital, ESNEFT
2. Senior members of the diabetes team at NEEDS, ESNEFT
3. Senior members of the diabetes team at West Suffolk hospital, WSNFT
4. Members of the Medicine management teams, IESCCG, NEECCG and WSCCG

Salient points:

The stake holders thank NICE for coming out with this important guideline which highlights several important aspects of management of Type-2 diabetes based on new developments. However, as a group, we felt that the NICE guideline was heavily weighted by the continued utilization of the incremental cost-effectiveness ratio (ICER) threshold which has led to non-consideration of key cardiovascular (CV) outcomes' data. Like many diabetes HCP colleagues nationwide, these aspects were notified to NICE by the diabetes centres at ESNEFT (as stakeholders' rebuttal) at the discussion stage but appears not to have had the necessary impact on the final outcome. The key omissions by NICE which has led to the development of this local guideline have been mentioned below:

- The NICE NG28 guideline is mostly based on ICER generated from individual trials –the majority of which were placebo controlled with very few trials being head to head either within class or in between various classes of treatment. We feel that due to heterogeneity amongst trial participants between various trials, such comparison can be affected by bias.

- Furthermore, the ICER thresholds generated by NICE was after breakdown of either 3-point major adverse cardiac events (MACE) which include: CV death, non-fatal MI, and non-fatal stroke or 4-point MACE (additionally includes hospitalisation for unstable angina). The ICER thresholds are disproportionately high for non-fatal strokes as compared to the other MACE events which have resulted in recognition of cardiovascular efficacy of the SGLT-2i class but not other drug classes

- The NICE NG28 guideline makes no mention of the 2019 ADA/EASD guideline [2] (Buse JB et al) which is currently being followed locally and in most parts of the UK al. https://doi.org/10.2337/dci19-0066 (accessed 6th March 2022). This guideline segregates type-2 diabetes patients into with or without CV disease/heart failure/chronic kidney disease or without. We feel that this segregation is based on current evidence and resonates with current clinical practice.

- Whilst we fully endorse the rationale of early adoption of SGLT-2i's in the treatment algorithm, NICE NG28 guideline does not specify the next class of drugs if SGLT-2i's are contraindicated (e.g. eGFR <20ml/min); cannot be tolerated (e.g. intolerance) or clinically unsafe (e.g. recurrent genital infections)

- The NICE NG28 guideline does not differentiate molecules within the SGLT-2i class with or without cardiovascular or heart failure or renal efficacy. In the ICS, we have elected not to use Ertugliflozin because of the lack of efficacy in the above non-glycaemic parameters; Cannon CP et al – VERTIS CV trial. [3]

- Despite the strong cardiovascular efficacy shown by injectable GLP-1Ra molecules of the human GLP-1 backbone (Dulaglutide/Semaglutide/Liraglutide), based on ICER thresholds, this class has been relegated to 4th line of therapy (i.e. if triple therapy with metformin and two other oral drugs is not effective). The local ICS feels that due to reasons mentioned above, it is not judicious to delay adoption of this class based simply on cost grounds. Similarly, we will not adopt the BMI criteria of 35kg/m2 for eligibility for GLP-1Ra class of therapies. This excludes Tirzepatide (NICE TA 924) since the latter is yet to demonstrate cardiovascular benefit but studies are currently on going e.g. SURPASS CVOT.

- The NICE NG28 guideline has divided Type-2 diabetes subjects into three categories: 1) Not at high CVD risk; 2) Chronic heart failure or established atherosclerotic CVD and 3) High risk of CVD QRISK2 of 10% or higher. There is a substantial body of evidence which suggests that type-2 diabetes irrespective of glycaemic control is associated with CV disease. Globally, overall CVD affects approximately 32.2% of all persons with T2DM. CVD is a major cause of mortality among people with T2DM, accounting for approximately half of all deaths [4]. In the UK, Research led by the University of Manchester found a 21% higher risk of cardiovascular disease and a 31% higher risk for heart failure hospitalisation for those with type 2 diabetes compared to people in the general population. We feel that this division adopted by NICE NG28 is surpassed the guidance from the 2019 ADA/EASD guideline and is more clinically appropriate [5].

- As per NICE TA guidance 924:
  Tirzepatide is recommended for treating type 2 diabetes alongside diet and exercise in adults when it is insufficiently controlled only if:
  - triple therapy with metformin and 2 other oral antidiabetic drugs is ineffective, not tolerated or contraindicated, and
  - they have a body mass index (BMI) of 35 kg/m2 or more, and specific psychological or other medical problems associated with obesity, or
  - they have a BMI of less than 35 kg/m2, and:
    - insulin therapy would have significant occupational implications, or
    - weight loss would benefit other significant obesity-related complications.

  (Use lower BMI thresholds (usually reduced by 2.5 kg/m2) for people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family backgrounds)
  - When reviewing the patient on GLP-1s to ensure that the patient is responding in line with NICE Guidance NG28.

References:

1. https://www.nice.org.uk/guidance/ta924 (assessed 15th November 2023)

2. https://www.nice.org.uk/guidance/ng28 (assessed 15th November 2023)

3. Melanie J. Davies, Vanita R. Aroda, Billy 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* 1 November 2022; 45 (11): 2753–2786. https://doi.org/10.2337/dci22-0034

4. Buse JB, Wexler DJ, Tsapas A et al. 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* 1 February 2020; 43 (2): 487–493. https://doi.org/10.2337/dci19-0066

5. Cannon CP, Pratley R, Dagogo-Jack S et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. N Engl J Med 2020; 383:1425-1435. DOI: 10.1056/NEJMoa2004967

6. Einarson, T.R., Acs, A., Ludwig, C. et al. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. Cardiovasc Diabetol 17, 83 (2018). https://doi.org/10.1186/s12933-018-0728-6

7. Wright AK, Suarez-Ortegon MF, Read SH et al. CirculationVolume 142, Issue 20, 17 November 2020; Pages 1925-1936. https://doi.org/10.1161/CIRCULATIONAHA.120.046783

8. https://www.ema.europa.eu/en/medicines/human/EPAR/mounjaro#product-information-section (assessed 15th November 2023)

NHS 75 Suffolk and North East Essex Integrated Care Board (ICB)

PHARMACOLOGICAL MANAGEMENT OF TYPE-2 DIABETES (based on NICE NG28 & ADA/EASD 2019 guidelines)

1st line therapy — **First line therapy is Metformin (± MR) in addition to lifestyle changes** *(optimal physical activity and weight reduction)*

Rescue therapy: For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

1st line therapy — **Consider early initiation of SGLT-2i if personalised glycaemic target not achieved**

SGLT-2i class: we encourage the use of only Dapagliflozin, Empagliflozin and Canagliflozin within this class

2nd line therapy — **Evaluate for Atherosclerotic cardiovascular disease (ASCVD), heart failure (HF) or chronic kidney disease (CKD) irrespective of HbA1c or BMI**

Yes

ASCVD PREDOMINATES

- **Preferably GLP-1Ra* with proven CVD benefit**
  OR
- **If not already on a SGLT2i: consider starting a SGLT-2i SGLT2i with proven CVD if eGFR is adequate**

Excludes Tirzepatide

HF or CKD PREDOMINATES

- **If not already on a SGLT2i: consider starting a SGLT-2i with evidence of reducing HF and/or CKD progression if eGFR is adequate**

OR

- **If SGLT2i is not indicated, then use GLP-1Ra with proven CVD**

If HbA1c above target
OR
Patient unable to tolerate
GLP-1Ra or SGLT2i

Choose agents demonstrating CV safety

- DPP-IV if not GLP-1Ra (**do not use Alogliptin or Saxagliptin with HF**)
- Basal insulin or other insulin combination therapies
- SU
- TZD (**do not use with HF**)

If ASCVD/HF/CKD status changes at any stage

No

3rd line therapy — **If HbA1c above individualised target, consider the agents below**

If hypoglycaemia prevention is a concern			If weight loss is a priority	Only HbA1c is a priority	
DPP-4i	GLP-1Ra	TZD	GLP-1Ra	SU	TZD

4th line therapy — **If HbA1c still above individualised target, consider any combinations of above OHA's or GLP-1Ra**

5th line therapy — **If HbA1c still above individualised target, consider adding basal insulin or appropriate insulin regime**

DPP-4 inhibitors:
Alogliptin
Linagliptin
Sitagliptin
Vildagliptin
Saxagliptin

SGLT-2i:
Dapagliflozin
Empagliflozin
Canagliflozin

GLP-1Ra:
Dulaglutide
Semaglutide
Liraglutide
Tirzepatide *(dual agonist)*

TZD:
Pioglitazone

SU:
Gliclazide
Glimepiride
Glibenclamide

Ver 3.0 –dated 22nd November 2023

Adapted from: 1. NICE NG28 Type 2 Diabetes guidelines and
2. ADA/EASD T2DM 2022 guidelines: Davies M et al. *Diabetes Care* 2022;45(11):2753–2786