The place of glucagon-like 1 peptide receptor agonists (GLP-1RAs) in the new NICE guidelines – what is going on?

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The article by Miles Fisher in this edition of the *British Journal of Diabetes* discusses cardiovascular outcome trials (CVOTs) which have examined the impact of GLP-1RAs in type 2 diabetes (T2DM). He queries 'why updated guidance from NICE…fails to acknowledge the evidence-based cardiovascular benefits'. Indeed, clinicians in the UK will be puzzled as to why this class of glucose-lowering therapy is now a first-line option in European and North American guidelines for people with T2DM at high cardiovascular risk, but remains well down the pecking order in NICE guideline (NG) 28.[1-3] This editorial will provide a short précis of the history of GLP-1RAs and NICE and try to explain the current impasse.

The National Institute of Clinical Excellence (NICE) was established in 1999 to 'diffuse the postcode lottery' of healthcare (for example, varying access to medicines according to where people lived) and serves the National Health Services (NHS) in England, Northern Ireland and Wales. Since its set-up, there have been two changes in name, the National Institute for Health and Clinical Excellence (2005) and the National Institute for Health and Care Excellence (2013) but the abbreviation of NICE has stood the test of time and is a globally recognised brand. Well over fifty countries world-wide access guidelines produced by NICE rather than doing their own in-depth assessment of new medicines.[4]

When it was launched, NICE inherited various guidelines for the management of T2DM, which were rebadged. It produced its first clinical guideline for T2DM (CG66) in 2008.[5] This was rapidly followed by the release of CG87 in May 2009, which was a short update on the 'newer agents' for blood glucose lowering.[6] This guideline included exenatide, given twice daily, which was the first GLP-1RA to be licensed in the UK (in 2007). Exenatide was positioned as a third-line 'alternative' add-on therapy to be considered after insulin, a thiazolidinedione or a dipeptidyl peptase-4 inhibitor and it was only sanctioned for use with metformin and a sulfonylurea. CG87 introduced the body mass index (BMI) cut-off of 35 Kg/m^2 for GLP-1RAs, which was not based on data from clinical trials but was the BMI at which the average cost of a long-acting insulin analogue was the same as BD exenatide. NICE also introduced 'stopping rules' where exenatide should be withheld when a reduction of at least 1% (11mmol/mol) in HbA_{1c} and weight loss of at least 3% initial body weight was not achieved after six months. Stopping rules have not been recommended for any other glucose-lowering class.

The next NICE guidance for the management of T2DM (NG28) was published in 2015 and is best remembered for the furore created by the recommendation of repaglinide as first-line treatment for people intolerant of metformin.[7,8] In the preceding six years, GLP-1RAs had been added to the glucose-lowering algorithm by means of single technology appraisals (TAs). These individual assessments by NICE had a more binding legal status than their guidelines, in that a positive TA recommendation mandated that funding should be made available by clinical commissioning groups. Thus, liraglutide (TA203, 2010), exenatide extended-release (TA248, 2012) and lixisenatide (2013) were all sanctioned for use, although NICE limited the dose of liraglutide to a maximum of 1.2mg OD on the basis that this dose had the same acquisition cost as BD exenatide.[9-11] The overall position of GLP-1RAs in the glucose-lowering algorithm was unchanged, however. They remained a third-line option for consideration after various triple oral combinations or insulin and were not even mentioned for people who could not tolerate metformin or for whom it was contra-indicated.

The first CVOT of a glucose-lowering therapy to demonstrate superiority was the EMPA-REG OUTCOME study of empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, and this trial was published three months before NG28 was launched in December 2015.[12] NG28 did not take into account these positive data, but this was not thought to be important since NICE had committed to regular updates every two years and more CVOT data were in the pipeline. Indeed, in 2016 there were positive CVOTs for both liraglutide (LEADER) and once-weekly semaglutide (SUSTAIN 6).[13,14] The positive superiority CVOT for dulaglutide (REWIND) was published in 2019 and there

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had also been a positive CVOT outcome for another weekly agent, albiglutide (HARMONY), although this drug was withdrawn in 2018 for commercial reasons.[15,16] Unfortunately, during this period of massive clinical advance, NICE did not perform any substantial T2DM updates.

The most recent NG28 update

In 2021 (again, six years on), NICE announced a consultation on an update of NG28. This was not a total revamp but focused on 'patient education, dietary advice, managing cardiovascular risk, managing blood glucose levels, and identifying and managing long-term complications'. The update was released on 31st March 2022, and it has certainly changed.[17] Based on the CVOTs and subsequent studies, SGLT2 inhibitors have moved up the treatment algorithm to being co-first line therapy (with metformin) for people with heart failure or established atherosclerotic cardiovascular disease (CVD) or those at high risk of CVD using the QRISK2 score. For those in whom metformin is contraindicated, SGLT2 inhibitors are recommended as first line. In contrast, the positioning of GLP-1RAs is essentially unchanged, with no mention of their CVOTs in the treatment algorithm and consideration only after triple oral therapy has failed to achieve glycaemic targets. NG28 recommendations 1.7.20 – 1.7.22 are almost verbatim from the 2015 offering, the BMI cut-off is still in place and stopping rules remain. Rather than being the default first-line injectable of the ADA/EASD consensus, GLP-1RAs remain the last glucose-lowering therapy choice for NICE (and, therefore, the NHS).

The obvious question is whether this is all down to money, since the GLP-1RAs are typically double the acquisition cost of SGLT2 inhibitors. However, NICE has been consistent throughout in making assessments of the incremental cost-effectiveness ratios (ICERs), with the current threshold for support being £20,000 - £30,000 per quality-adjusted life-year (QALY) gained. According to data available on its website, the ICERs for SGLT2 inhibitors in people with T2DM at 'high CV risk – prior event' (recommended for use in NG28), are £15,380 - £31,165, whilst the ICER for semaglutide (injection) (not recommended) is £21,916.[18]

To date, for glucose lowering, NICE has dealt with classes rather than individual agents within a class. So, given the large variation in ICERs for different GLP-1RAs, it may seem reasonable not to be swayed by a very favourable outcome for one drug. However, there have now been fourteen head-to-head studies within the GLP-1RA class, confirming that there are substantial differences in HbA1c lowering and weight loss; these would be expected to manifest as variation in ICERs.[19] In addition, NICE should have been able to refer to data from its own TAs of the modern once-weekly GLA-1RAs which are now most commonly initiated in the UK. Unfortunately, the appraisals of subcutaneous semaglutide (TA10438) and dulaglutide (TA10439), proposed in 2018, were not performed: they were due to be incorporated into the update of NG28 but this did not happen.[20,21]

Key messages

- A partial update of NICE guideline (NG) 28 was released in 2022, over six years after the initial publication.
- The place of GLP-1RAs in the management of type 2 diabetes in NG 28 has not been altered by the positive results from cardiovascular outcome trials.
- NG 28 is now inconsistent with modern European and North American recommendations for the management of type 2 diabetes

Conclusion

Where does this leave us? NICE recently announced another update of NG28, this time focusing on 'the section on drug treatment'. It states that whereas 'the previous update of the guideline focused on the cardiovascular benefits of drug treatment, in this update the drug treatment section will be updated in full.' No-one should imagine, however, that incorporation of data and costings from CVOTs will be a simple task. The trials vary in many ways, such as inclusion criteria, rescue medication protocols, study durations and endpoint definitions. Ideally, the development of a new economic model will require access to patient-level data and, at present, these are not available. In any event, the process will be slow, with guidance consultation planned for June-August 2024 and an expected publication date of 4th December 2024. Perhaps a biosimilar of a GLP-1RA with proven CV benefit will be available by then.[22]

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ERRATUM

Imeglimin, a novel, first in-class, blood glucose-lowering agent: a systematic review and meta-analysis of clinical evidence

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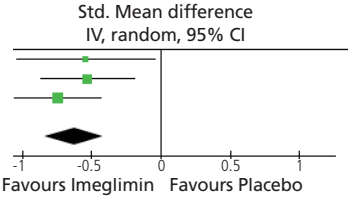
In the article listed above, there was an error in Figure 2. Please find below the corrected figure.

Figure 2. Forest plot showing meta-analysis of imeglimin versus placebo for (a) HbA_{1c} (%) and (b) fasting plasma glucose levels (mmol/L) using a random-effect model. Risk of bias assessment is also included

a)

Study or subgroup	Imeglimin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean difference IV, random, 95% CI	Year
Pirags et al. 2012 (1)	-0.18	0.9	31	0.31	0.88	33	17.5%	-0.54 (-1.04, -0.04)	2012
Fouqueray et al. 2013	-0.65	0.82	68	-0.21	0.83	69	37.6%	-0.53 (-0.87, -0.19)	2013
Fouqueray et al. 2014	-0.6	0.99	81	0.12	0.93	88	44.8%	-0.75 (-1.06, -0.43)	2014
Total (95% CI)			180			190	100.0%	-0.63 (-0.84, -0.42)	

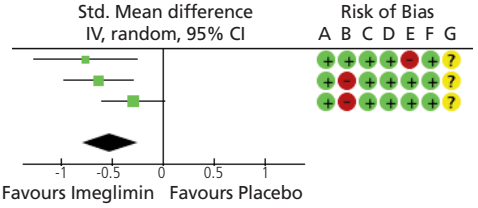
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.98$, df = 2 (p = 0.61); $I^2 = 0\%$
Test for overall effect: z = 5.90 (p<0.00001)



b)

Study or subgroup	Imeglimin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean difference IV, random, 95% CI	Year
Pirags et al. 2012 (1)	-1.02	2.38	31	0.78	2.27	33	21.9%	-0.77 (-1.27, -0.26)	2012
Fouqueray et al. 2013	-0.91	1.96	67	0.36	2.02	71	36.6%	-0.63 (-0.98, -0.29)	2013
Fouqueray et al. 2014	-0.93	2.79	81	-0.11	2.72	88	41.5%	-0.30 (-0.60, -0.01)	2014
Total (95% CI)			179			192	100.0%	-0.52 (-0.80, -0.24)	

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.36$, df = 2 (p = 0.19); $I^2 = 41\%$
Test for overall effect: z = 3.68 (p=0.0002)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

(1) SD absent therefore average variance of other studies used in lieu (this is likely an overestimate of variance given Figure 2 in original paper)