Association of British Clinical Diabetologists

Sandwell and West Birmingham Hospitals NHS Trust

NICE guidelines *versus* clinical practice – GLP-1 receptor agonists in type 2 diabetes: the ABCD nationwide audits

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on behalf of the ABCD Nationwide exenatide* and liraglutide† audit contributors

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Introduction

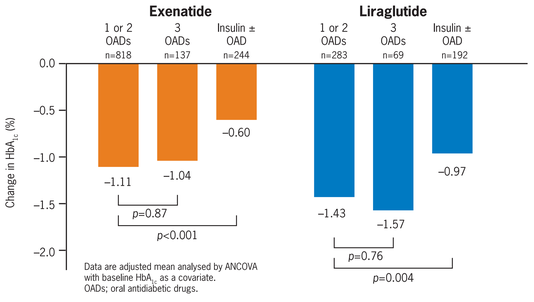
In conducting two nationwide audits on the use of the glucagon-like pepide-1 receptor agonists (GLP-1RA) exenatide and liraglutide in the UK,[1] we found that deviations from NICE guidelines were common. Using data from both audits, which had a combined total of 12,955 patients, we evaluated these treatment decisions as well as critically appraised the NICE guidelines.

Findings

We found that in their present form, the NICE guidelines for GLP-1RAs essentially prevent their use in patients with more advanced diabetes who still require effective treatment. Specifically:

- More clinical trials and cost-effectiveness analyses are needed in obese patients with more advanced diabetes. The issue is not the comparative costs of third-line diabetes treatment, but that of the comparative costs and effectiveness (Figure 1) of patients already on third-line therapy who require treatment intensification (such as either by escalating insulin doses or using GLP-1RAs). Creative solutions such as an agreement to combine cheaper human insulin with GLP-1RAs could be explored but requires considerations of the potential disadvantages of older insulins compared with insulin analogues.
- The addition of GLP-1RAs to three oral antidiabetic drugs was as effective as adding them to one or two drugs (Figure 1) and should be considered as a viable treatment algorithm.

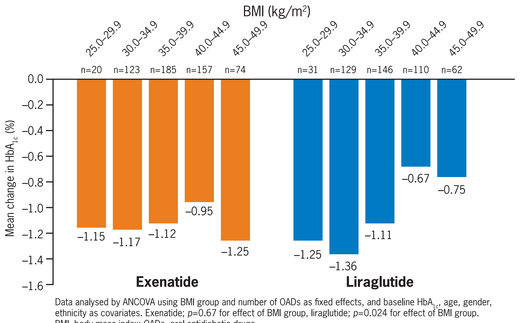
Figure 1. HbA_{1c} change at 20–32 weeks with exenatide and liraglutide as add-on therapy to patients on 1 or 2 OADs, on 3 OADs, or on basal or biphasic insulin.



Data are adjusted mean analysed by ANCOVA with baseline HbA_{1c} as a covariate.
OADs; oral antidiabetic drugs.

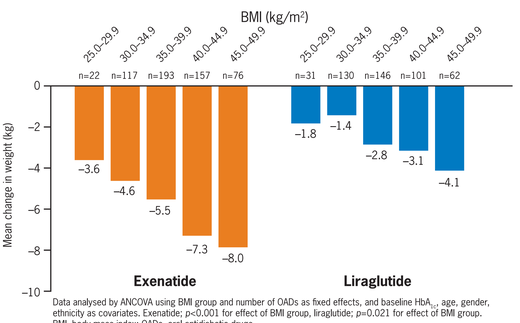
- We would caution clinicians against substituting concurrent diabetes treatment to appear to adhere to guidelines when GLP-1RAs are started due to the risk of glycaemic deterioration.[2]
- The general requirement by NICE for patients' BMI to be greater than 35 kg/m² is not strictly evidenced-based, and this strategy to improve cost-effectiveness may be counter-productive if glycaemic improvement is diminished in more obese patients (Figures 2 and 3).

Figure 2. HbA_{1c} change at 20–32 weeks with exenatide and liraglutide as add-on therapy to non-insulin-treated patients, results stratified by baseline BMI.



Data analysed by ANCOVA using BMI group and number of OADs as fixed effects, and baseline HbA_{1c}, age, gender, ethnicity as covariates. Exenatide; p=0.67 for effect of BMI group, liraglutide; p=0.024 for effect of BMI group.
BMI, body mass index; OADs, oral antidiabetic drugs.

Figure 3. Weight change at 20–32 weeks with exenatide and liraglutide as add-on therapy to non-insulin-treated patients, results stratified by baseline BMI.



Data analysed by ANCOVA using BMI group and number of OADs as fixed effects, and baseline HbA_{1c}, age, gender, ethnicity as covariates. Exenatide; p<0.001 for effect of BMI group, liraglutide; p=0.021 for effect of BMI group.
BMI, body mass index; OADs, oral antidiabetic drugs.

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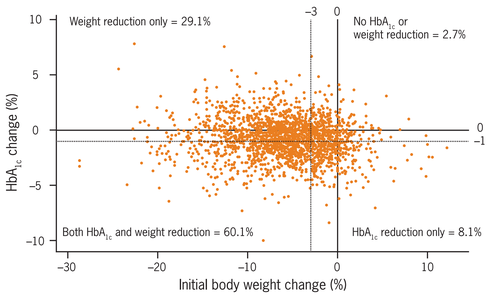
- Few patients also meet the criteria for continuing GLP-1RA therapy (Figure 4). We propose that patients who have achieved significant HbA_{1c} reduction but not weight reduction be allowed to continue GLP-1RA treatment.

Figure 4a. Scatterplot of HbA_{1c} change and intial body weight change at 20–32 weeks of 1882 patients treated with exenatide.



Dotted line indicates criteria of ≥1% HbA_{1c} reduction and ≥3% initial body weight reduction require by NICE for continuation of therapy – while 60.1% of patients achieved both HbA_{1c} and weight reduction, only 28.6% achieved this to the criteria level set by NICE.

Figure 4b. Scatterplot of HbA_{1c} change and initial body weight change at 20–32 weeks of 1023 patients treated with liraglutide

Dotted line indicates criteria of ≥1% HbA_{1c} reduction and ≥3% initial body weight reduction require by NICE for continuation of therapy – while 59.3% of patients achieved both HbA_{1c} and weight reduction, only 25.0% achieved this to the criteria level set by NICE.

- The NICE criterion of ≥1% HbA_{1c} reduction as a requirement for continued GLP-1RA treatment is unfair due to favouring patients with higher baseline HbA_{1c} (Table 1). Hence, we conclude that a measure of HbA_{1c} reduction indexed to a patient's baseline HbA_{1c} is probably the fairest method to determine response, such as achieving an HbA_{1c} reduction that is better than the median HbA_{1c} reduction of a baseline HbA_{1c} group. Based on the results of Table 1, a simplified but graded criterion for non-insulin-treated patients may be that of a requirement of >0.5% reduction if HbA_{1c} was <8.0%, >1.0% if HbA_{1c} was 8.0–9.0% and >1.5% if HbA_{1c} was >9.0%.

Table 1. Median HbA_{1c} change, proportion of patients achieving HbA_{1c} reduction of ≥1% and proportion of patients achieving target HbA_{1c} of 7% among patients treated with liraglutide in the ABCD audit; results stratified by baseline HbA_{1c} and use of insulin.

	Baseline HbA_{1c}							
	7.0–7.9	**8.0–8.9**	**9.0–9.9**	**10.0–10.9**	**11.0–11.9**	**12.0–12.9**	**13.0–13.9**	***P* value**
Non-insulin-treated								
n	91	158	161	106	60	35	11	
Median HbA_{1c} change, (%)	−0.7 [−1.1,−0.1]	−1.1 [−1.7,−0.5]	−1.4 [−2.2,−0.4]	−1.9 [−3.2,−0.9]	−2.6 [−3.9,−1.6]	−3.1 [−1.3,−4.5]	−2.0 [−0.3,−4.9]	<0.001
Proportion achieving ≥1% reduction, n (%)	30 (33.0)	95 (60.1)	103 (64.0)	77 (72.6)	51 (85.0)	28 (80.0)	8 (72.7)	<0.001
Proportion achieving HbA_{1c} of 7%, n (%)	50 (55.0)	58 (36.7)	35 (21.7)	25 (23.6)	11 (18.3)	4 (11.4)	1 (9.1)	<0.001
Insulin-treated								
n	73	124	156	98	61	35	10	
Median HbA_{1c} change, (%)	−0.2 [−0.7,0.4]	−0.5 [−1.2,0.3]	−1.1 [−2.0,−0.2]	−1.3 [−2.6,−0.5]	−1.3 [−2.5,−0.5]	−1.8 [−3.4,−0.6]	−3.6 [−4.7,−1.6]	<0.001
Proportion achieving ≥1% reduction, n (%)	11 (15.1)	41 (33.1)	82 (52.6)	61 (62.2)	36 (59.0)	24 (68.6)	9 (90.0)	<0.001
Proportion achieving HbA_{1c} of 7%, n (%)	28 (38.4)	18 (14.5)	21 (13.5)	8 (8.2)	3 (4.9)	1 (2.9)	2 (20.0)	<0.001

Median HbA_{1c} change results are shown as median [interquartile range].
Results show patients are more likely to achieved ≥1% HbA_{1c} reduction when baseline HbA_{1c} is higher and conversely more likely to achieve target HbA_{1c} of 7% if baseline HbA_{1c} is lower.

References

1. For findings from the ABCD nationwide exenatide and liraglutide audits, respectively, see:
www.diabetologists.org.uk/GLP1_Audits/PresentationsPostersAbstractsExenatide.htm
www.diabetologists-abcd.org.uk/GLP1_Audits/PresentationsPostersAbstractsLiraglutide.htm
2. Thong KY, Jose B, Blann AD, Cull ML, Mills AP, Sathyapalan T, Walton C, Ryder RE. Response at 3 months to insulin dose decisions made at exenatide initiation in the Association of British Clinical Diabetologists (ABCD) nationwide exenatide audit. *Diabetes Res Clin Pract* 2011; 93: e87-91.
3. Ryder REJ, Thong KY, Blann AD, Phillips SM, Barwell ND, Kelly CJG, Semple C, Cull ML, Sen Gupta P, and the ABCD nationwide liraglutide audit contributors. Liraglutide pancreatitis: The ABCD nationwide liraglutide audit. *Br J Diabetes Vasc Dis* 2013; 13: 253–259.

Acknowledgements

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