



Injectable semaglutide and reductions in HbA1c and weight in the real world in people switched from alternative glucagon-like peptide-1 receptor agonists

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Funding information

NovoNordisk

Abstract

The ABCD semaglutide audit was designed to capture the routine clinical outcomes of people commenced on semaglutide in the UK. Previous work showed differential reductions in HbA1c and weight dependent on previous glucagon-like peptide-1 receptor agonist (GLP-1RA) exposure. The analysis, in this research letter, shows that decreases in HbA1c and weight associated with semaglutide occur irrespective of previous GLP-1RA use. However, HbA1c reductions were less if switched from dulaglutide or liraglutide and weight changes were attenuated if switched from dulaglutide or exenatide, potentially suggesting differing potencies between GLP-1RAs. Dedicated studies with head-to-head comparisons are needed to confirm these findings.

KEYWORDS

GLP-1 analogue, observational study, type 2 diabetes

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TABLE 1 Baseline characteristics of the population and of each GLP-1RA subgroup

Characteristic	All	GLP-1RA naïve	GLP-1RA: all	Dulaglutide	Liraglutide	Exendin	P value*
HbA1c, %	9.3 ± 1.7	9.5 ± 1.7	8.9 ± 1.6	9.1 ± 1.5	8.8 ± 1.7	8.9 ± 1.6	.007 [†]
Weight, kg	107.3 ± 23.1	106.7 ± 22.4	109.0 ± 25.0	109.7 ± 24.7	110.5 ± 24.6	104.8 ± 26.3	.34
BMI, kg/m ²	37.3 ± 7.3	37.1 ± 7.5	37.9 ± 6.8	38.0 ± 6.9	38.4 ± 6.4	36.6 ± 7.4	.34
Age, y	56.3 ± 10.6	59.4 ± 10.7	59.0 ± 10.3	59.0 ± 10.1	57.9 ± 10.6	61.5 ± 9.3	.26
Gender, % male	50.1	50.0	50.25	46.2	48.0	51.1	.92
Diabetes duration, y	11 (6-15)	10 (6-15)	13 (10-16)	12 (8-16)	12 (10-15)	14 (11-17)	.003 [†]
Follow-up duration, mo	6.8 (4.4-9.9)	6.4 (4.3-9.4)	8.1 (5.3-10.8)	6.1 (4.0-9.4)	9 (5.5-11.7)	8.3 (5.5-10.8)	<.001 [†]
SGLT2i use, % (n)	25.5 (195)	28.5 (162)	16.8 (33)	23.1 (12)	10.0 (10)	24.4 (11)	.001

Note: Data are reported as mean ± SD, median (IQR), or % (n =).

Abbreviations: BMI, body mass index; GLP1-RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

*P value from ANOVA or Chi-squared tests comparing GLP-1RA-naïve, dulaglutide, liraglutide and exendin (combined exenatide and lixisenatide) groups.

[†]Differences between liraglutide and GLP-1RA-naïve subgroups noted, but no differences between any other subgroups to Bonferroni-corrected $P < .05$ level.

TABLE 2 Changes in HbA1c (%) and weight (kg) from baseline, stratified by previous GLP-1RA use, including pooled previous GLP-1RA group and entire population

Group	HbA1c, %			Weight, kg		
	n	Mean change (95% CI)	P value	n	Mean change (95% CI)	P value
All	664	-1.2 (-1.3, -1.1)	<.001	586	-4.4 (-4.8, -3.9)	<.001
GLP-1RA naïve	483	-1.4 (-1.5, -1.2)	<.001	430	-4.8 (-5.4, -4.3)	<.001
GLP-1RA: all	181	-0.7 (-1.0, -0.6)	<.001	156	-3.2 (-4.0, -2.4)	<.001
Dulaglutide	51	-0.6 (-1.0, -0.2)	.005	32	-1.5 (-3.2, 0.1)	.071
Liraglutide	93	-0.8 (-1.1, -0.5)	<.001	85	-4.2 (-5.3, -3.2)	<.001
Exendin group ^a	37	-1.0 (-1.4, -0.5)	.001	40	-3.0 (-5.4, -0.7)	.014

Abbreviation: GLP1-RA, glucagon-like peptide-1 receptor agonist.

^aCombined exenatide and lixisenatide group.

1 | BACKGROUND

The glucagon-like peptide-1 receptor agonist (GLP-1RA) class is widely prescribed for type 2 diabetes. Randomized control trial evidence from the SUSTAIN trials showed improvements in HbA1c and weight with semaglutide compared with placebo, exenatide (once-weekly), and dulaglutide (0.75 and 1.5 mg, once-weekly) injections.¹⁻³ Indirect comparisons with higher dose dulaglutide using pooled data from AWARD-11 and SUSTAIN 7 have been undertaken.^{2,4} These suggested comparable HbA1c reductions between semaglutide and higher doses of dulaglutide (3 and 4.5 mg), but suggested that semaglutide remained superior for weight loss. Semaglutide was also found to be superior to weight loss to liraglutide in the STEP8 randomized control trial.⁵ These findings are further supported by a systematic review and network meta-analysis of randomized controlled trials (RCTs) that found semaglutide reduces HbA1c and weight more effectively than other GLP-1RAs.⁶ However, efficacy in practice may not mirror RCT results because trial eligibility criteria are often restricted, and support for participants is seldom representative of

routine practice. Furthermore, no RCTs have investigated the efficacy of semaglutide when switching from another GLP-1RA. Real-world observational data suggest that semaglutide is associated with significant reductions in HbA1c and weight, although these reductions appear to be smaller in those switched from alternative GLP-1RA drugs.⁷⁻¹⁰ A larger study looking at only those who switched from either dulaglutide or exenatide (both once-weekly) showed further HbA1c and weight reductions of 0.8% and 2.8 kg, respectively¹¹. While this provides some indication that the potential superiority of semaglutide translates into the real world, the studies we have identified incorporating head-to-head comparisons on switching are limited either by their small numbers or by the absence of a GLP-1RA-naïve group to provide a comparison.

The Association of British Clinical Diabetologist (ABCD) audit programme captures baseline and follow-up data from routine clinical practice in centres across the UK. The aim of this analysis was to contrast HbA1c and weight changes associated with semaglutide use among those previously receiving GLP-1RA therapy and in those GLP-1RA naïve, including head-to-head

comparison with all commonly encountered GLP-1RA drugs in UK practice.

2 | METHODS

Data were extracted from the ABCD nationwide semaglutide audit and prepared for analysis, providing baseline and relevant follow-up data for HbA1c and/or weight. Comparisons were made between those switched from dulaglutide, liraglutide, and exendin-based GLP-1RA (combining data from individuals on either exenatide or lixisenatide), as well as a pooled analysis of all previous GLP-1RA users and those who were GLP-1RA naïve. Statistical analysis was performed in Stata 16 using paired *t* tests and ANOVA with Bonferroni corrections. Data were not available for doses of dulaglutide greater than 1.5 mg weekly, nor for oral semaglutide.

3 | RESULTS

Of 1625 users in the audit, 765 had sufficient data available for analysis. Of these, 568 (74.3%) were GLP-1RA naïve. The remainder had been switched from liraglutide (100, 13.1%), dulaglutide (52, 6.8%), or exendin-based GLP-1RAs (45, 5.9%). Baseline characteristics (mean \pm SD, comparing GLP-1RA naïve vs. previous GLP-1RA use) were: age 59.4 ± 10.7 versus 59.0 ± 10.3 years ($P = .66$); HbA1c $9.5\% \pm 1.7\%$ versus $8.9\% \pm 1.6\%$ ($P = .001$); weight 106.7 ± 22.4 versus 109.0 ± 25.0 kg ($P = .24$), and body mass index 37.1 ± 7.5 versus 37.9 ± 6.8 kg/m² ($P = .21$). The median follow-up was 6.8 (IQR 4.4–9.9) months. The characteristics of each GLP-1RA subgroup are summarized in Table 1, with baseline differences between groups compared with ANOVA or Chi-squared tests as relevant. Differences were noted between the liraglutide and GLP-1RA-naïve subgroups in terms of baseline HbA1c (lower with liraglutide), diabetes duration, and follow-up time (both longer with liraglutide). A lower proportion of people taking liraglutide were using sodium-glucose co-transporter-2 inhibitors (SGLT2i) than expected. No other baseline differences between groups were noted.

At follow-up, significant changes in HbA1c (-1.2% ; 95% CI -1.1% , -1.3% ; $P < .001$) and in weight (-4.4 kg; 95% CI -3.9 , -4.8 , $P < .001$) were observed in the entire cohort. HbA1c and weight changes stratified by previous GLP-1RA are displayed in Table 2.

4 | CONCLUSIONS

Semaglutide use was associated with significant HbA1c reductions in all groups. In comparison with the GLP-1RA-naïve group, HbA1c reduction was significantly attenuated in people switched from dulaglutide ($P = .005$) and liraglutide ($P = .01$), but not from other GLP-1RAs.

Semaglutide use was associated with significant weight loss in all groups other than those previously on dulaglutide. In comparison with the GLP-1RA-naïve group, the magnitude of weight change was less

in people switched from dulaglutide ($P = .014$) and the exendin-based GLP-1RAs ($P = .033$), but not from liraglutide.

Our analysis sheds new light on the real-world efficacy of semaglutide in comparison with other GLP-1RAs and is the first to include comparisons with all commonly encountered GLP-1RA drugs, with larger numbers than included in other studies and with the addition of a GLP-1RA-naïve group for additional comparison. We observed statistically significant HbA1c reductions in patients switched to semaglutide from all other GLP-1RAs. We also observed significant weight loss in patients switched from liraglutide or exendin-based GLP-1RAs, but not in those previously taking dulaglutide. The relative magnitude of these changes may reflect differences between semaglutide and other GLP-1RAs in efficacy, tolerability or adherence, and/or other potentially confounding patient cohort-related factors in this retrospective, observational study. Such factors could include baseline SGLT2i use, follow-up interval, and/or those for which data were unavailable, including duration of prior treatment, and the magnitude of prior HbA1c and weight change with alternative GLP-1RAs before the switch to semaglutide.

It should be noted that the liraglutide group had longer follow-up periods and higher HbA1c at baseline, although this does not explain why HbA1c reductions would be attenuated in this group (if anything the opposite might be expected) and it is unlikely to account fully for weight loss in this group being somewhat similar to GLP-1RA-naïve individuals. We hypothesize that adherence to daily liraglutide injections might be less than to weekly injections of either dulaglutide or semaglutide, but cannot test this within the available data.

Our findings are broadly comparable with those from existing real-world evidence and RCTs.^{1-3,5,7-10} However, the mean weight and HbA1c in our study were greater than those of RCT cohorts, reflecting current UK practice in management of type 2 diabetes that prioritizes GLP-1RA use for people who are probable to benefit from significant weight loss. We were not able to assess the relative effectiveness of semaglutide doses above 1.0 mg once weekly, nor of oral semaglutide, nor doses of dulaglutide above 1.5 mg once weekly, because these were not licensed at the time of data collection. A further limitation of our study is the use of paired *t* tests to compare change within each group separately, rather than a more complex statistical analysis with cross-group comparisons. The latter approach would be appropriate for a randomized clinical trial or meta-analysis but, in this retrospective observational study, would make excessive assumptions about the underlying data.

More work will be needed to compare the efficacy of the expanding dose range of semaglutide with forthcoming dual-receptor agonists and with the recently approved higher doses of dulaglutide. Another important comparison, which may be difficult to achieve, concerns relative efficacy in cardiovascular risk reduction. Our work may nevertheless help clinicians and their patients to choose between GLP-1RAs, and to decide whether to switch from one GLP-1RA to another if further reduction in HbA1c and/or weight is required. It also provides further evidence of the extent to which the findings of RCTs and network meta-analyses may be translated into routine clinical practice.

CONFLICT OF INTEREST

TSJC has received speaker fees/support to attend meetings from NovoNordisk, Sanofi, and Abbott Diabetes Care. BCTF has acted as a consultant, speaker, and/or received support to attend meetings from Abbott Diabetes, AstraZeneca, Boehringer Ingelheim, Eli Lilly, GSK, Janssen, Medtronic, MSD, Napp, Novo Nordisk, and Sanofi. The other authors have no other relevant interests to declare.

AUTHOR CONTRIBUTIONS

All authors contributed significant numbers of patients to the audit programme and provided editorial feedback on the manuscript. The analysis was performed by TSJC and the manuscript was written largely by TSJC with significant input from BCTF, II and REJR.

FUNDING INFORMATION

The ABCD semaglutide audit is supported by an unrestricted grant from NovoNordisk.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.14701>.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Crabtree TSJ, Adamson K, Reid H, et al. Injectable semaglutide and reductions in HbA1c and weight in the real world in people switched from alternative glucagon-like peptide-1 receptor agonists. *Diabetes Obes Metab.* 2022;1-4. doi:10.1111/dom.14701