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BRIEF REPORT

Real-World Use of Oral and Subcutaneous Semaglutide in Routine Clinical Practice in the UK: A Single-Centre, Retrospective Observational Study

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ABSTRACT

***Introduction*:** Semaglutide, the only glucagon-like peptide-1 receptor agonist (GLP-1 RA) available in subcutaneous and oral formulation for treatment of type 2 diabetes (T2D), has demonstrated clinically significant improvements in glycaemic control and weight in clinical trials. This study aimed to gain insights into the use of both formulations and evaluate their clinical effectiveness in a secondary care clinic in Wales.
***Methods*:** This was a retrospective observational analysis of adults with T2D initiated on oral or subcutaneous semaglutide. Changes from baseline in glycated haemoglobin (HbA_{1c}), weight and other metabolic parameters were evaluated.
***Results*:** At baseline, participants ($n = 103$) had a mean age of 57.3 years, mean HbA_{1c} of 79.1 mmol/mol (9.38%), mean weight of 111.8 kg and body mass index (BMI) of 39.6 kg/m^2 (no statistically significant differences between oral and subcutaneous groups). At 6-month follow-up, statistically significant improvements in HbA_{1c} (− 19.3 mmol/mol [− 1.77%] and − 20.8 mmol/mol [− 1.90%]), body weight (− 9.0 kg and − 7.2 kg), and BMI (− 3.3 kg/m^2 and − 2.5 kg/m^2) were observed for oral and subcutaneous semaglutide, respectively. No statistically significant differences between the formulations were observed, and safety profiles were comparable.
***Conclusions*:** Both formulations of semaglutide provided clinically and statistically significant reductions in HbA_{1c} and weight in real-world practice. Oral GLP-1 RA may offer a practical and effective option for the management of T2D.

Keywords: GLP-1 RA; Primary care; Real-world evidence; Secondary care; Semaglutide; Type 2 diabetes

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Key Summary Points
There is a lack of real-world evidence on the use and effectiveness of oral semaglutide.
This was a retrospective, observational study evaluating oral and subcutaneous semaglutide in real-world clinical practice.
People initiated on glucagon-like peptide-1 receptor agonists in this secondary care clinic typically had poor glycaemic control (glycated haemoglobin ≥ 8.0%) and body mass index > 30 kg/m^2.
Oral and subcutaneous semaglutide were both shown to be clinically effective in real-world practice.
A number of factors, including patient choice, should be taken into consideration when deciding on which formulation to use in practice.

INTRODUCTION

Type 2 diabetes (T2D) is a progressive disease with complex underlying pathophysiology. People with T2D experience worsening glycaemic control and the development of complications over time [1, 2]. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) guidelines state that early treatment intensification in T2D is vital for achieving good long-term outcomes, especially for people who present with glycated haemoglobin (HbA_{1c}) levels > 16.4 mmol/mol (1.5%) above target [1, 2]. The benefits of early intensification, including significantly reduced risk of complications and mortality, have been shown to persist for at least a decade after treatment intervention (the legacy effect) [3, 4].

The UK National Institute for Health and Care Excellence (NICE) recommends a glycaemic target of $HbA_{1c} \leq 53$ mmol/mol (7.0%) for people with T2D on medications associated with hypoglycaemia, and a target of $HbA_{1c} \leq 48$ mmol/mol (6.5%) otherwise [5, 6]. However, in the UK in 2020–2021, only 63.4% of people with T2D met a target of $HbA_{1c} \leq 58$ mmol/mol (7.5%) [5]. These data are evidence of 'therapeutic inertia', or failure to intensify therapy in a timely manner [7]. The 2022 ADA/EASD consensus recommends a patient-centred approach for the management of T2D that considers cardiovascular disease (CVD) history, weight, hypoglycaemic risk, treatment cost and other patient-related factors.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are among the most effective drugs for treatment of T2D, reducing HbA_{1c} and weight whilst presenting a comparatively low risk of hypoglycaemia. Some GLP-1 RAs also have proven cardiovascular (CV) benefits [2, 8]. GLP-1 RAs are recommended when oral therapy does not adequately control HbA_{1c}, and are also a preferred option for chronic weight management in people living with T2D and overweight or obesity. For people with established CVD or multiple CVD risk factors, a GLP-1 RA with proven CV benefit is the first choice to reduce risk of major adverse CV events (MACE) [1, 2].

Semaglutide is a GLP-1 RA available in two formulations for T2D: once-weekly subcutaneous injection and once-daily oral tablet (the first GLP-1 RA developed for oral administration). Efficacy and safety of semaglutide in T2D are well documented: both formulations demonstrated significantly lower HbA_{1c} and body weight versus various comparators in landmark phase 3 clinical trial programs (SUSTAIN and PIONEER) [9–11]. Additionally, they have demonstrated CV safety, with the subcutaneous formulation significantly reducing risk of MACE along with improving CV risk factors such as systolic blood pressure and cholesterol levels [9, 10, 12]. Semaglutide has a comparable adverse event (AE) profile to other GLP-1 RAs [9, 10, 13–15].

Oral semaglutide provides an option for people who are reluctant to initiate injectable therapy [9]. Anxiety around injections and perceived inconvenience of injectable therapies are commonly cited reasons for poor adherence in people with diabetes [16–18]. Oral semaglutide therefore has the potential to encourage both earlier use of GLP-1 RAs and improve adherence. Additionally, primary care providers may find the oral formulation simpler to prescribe,

since advice on proper injection technique is not required [19].

With marketing authorisation first granted only in 2020, there is a lack of real-world evidence on the use and effectiveness of oral semaglutide [20]. This analysis aimed to gain insights into the use of the two semaglutide formulations and to evaluate their clinical effectiveness in a secondary care setting in Wales.

METHODS

All subjects with T2D who were initiated on either subcutaneous or oral semaglutide between August 2020 and February 2022 at secondary care diabetes clinics in the Princess of Wales Hospital (Bridgend) were identified using a local electronic database ($n = 103$).

Key deciding factors for initiation of oral or subcutaneous semaglutide included: patient preference (fear of injection); age and comorbidity limiting dexterity and causing anxiety around injection device; dietary patterns (oral formulation requires fasting for optimal absorption); and any factors which could potentially affect adherence to daily medication. The subcutaneous option was offered mainly to people with established CVD, high CV risk and/or BMI > 35 kg/m^2 and HbA_{1c} > 75 mmol/mol (9.0%).

Data were collected from pre-initiation (baseline) and 6 months post-initiation (follow-up) assessments, as part of routine clinical practice. In addition, all subjects attended four-weekly telephone follow-up visits with a healthcare assistant which aimed to reduce discontinuation and offer additional time to stabilise before subsequent dose escalation. Dose escalation was conducted according to the product label, subject to tolerability and physician discretion. Treatment discontinuations (temporary and permanent) were recorded.

Demographic characteristics, concomitant medication and comorbidities were collected at baseline as part of the initial consultation. Change from baseline at 6-month follow-up in variables including HbA_{1c}, weight/BMI, estimated glomerular filtration rate (eGFR), lipid profile, and liver function were examined. Subjects were questioned about side effects during the four-weekly follow-up calls and at the end of the 6-month follow-up period.

The effect of semaglutide in subgroups defined by (1) baseline glycaemic control (2) baseline BMI, and (3) age was evaluated. For the glycaemic control groups, subjects with baseline $HbA_{1c} < 75$ mmol/mol (9.0%) were compared with those with baseline $HbA_{1c} \geq 75$ mmol/mol (9.0%), the level at which NICE recommends consideration of insulin therapy [6].

For the BMI groups, subjects with baseline BMI ≥ 35.0 kg/m^2 were compared with those with baseline BMI < 35.0 kg/m^2. The BMI cut-off of 35.0 kg/m^2 was used in line with NICE guidance, which recommends considering GLP-1 RAs for people with BMI ≥ 35.0 kg/m^2 [6]. For age subgroups, we compared subjects aged < 60 years with those aged ≥ 60 years, as this was close to the median age of the cohort.

Statistical Analysis

Statistical analysis was performed using Stata 17 (Stata Corp. 2021). For each variable, all patients with values at baseline and follow-up were included in the analysis. Results for continuous variables are presented as mean and standard deviation (SD). The paired *t* test was used to compare mean values of continuous variables at baseline and follow-up. An unpaired *t* test was used to compare mean values of continuous variables between the two treatment arms, and the chi-squared test or the Fisher's exact test were used to compare categorical variables between the two arms.

A linear mixed model was estimated for each outcome with an intercept term and fixed effects for treatment (subcutaneous, oral), data collection time-point (baseline, follow-up), and an interaction term between the treatment and time-point. The anonymized person identifier was included as a random effect, allowing the person level intercept to vary. The coefficient for the interaction term and the corresponding 95% confidence intervals (CIs) at follow-up were used to calculate estimated treatment differences (ETDs).

Two-sided significance values (p values) or 95% CIs of the changes from baseline or ETDs were obtained from complete case analysis, i.e., participants with missing data of interest were excluded.

Compliance with Ethics Guidelines

Ethics committee approval was not required, as this analysis was conducted as part of a service-based evaluation project to examine the effects of semaglutide therapy, which is routine in our local practice. Only de-identified secondary data were used. Approval from the head of department was received.

RESULTS

Baseline Characteristics

The study cohort comprised 103 individuals (Table 1). Average age was 57.3 ± 10.5 years, and 48% were male. Mean HbA_{1c} was 79.1 ± 5.4 mmol/mol (9.38 ± 1.41%) at baseline, mean body weight was 111.8 ± 26.3 kg and mean BMI was 39.6 ± 9.1 kg/m^2.

The two treatment groups were comparable across all baseline characteristics. The oral semaglutide group comprised 53 individuals with average age 58.5 ± 10.4 years, and the subcutaneous semaglutide group comprised 50 individuals with average age 56.0 ± 10.7 years. Baseline HbA_{1c} (78.0 ± 14.1 mmol/mol [9.28 ± 1.29%] and 80.1 ± 16.9 mmol/mol [9.48 ± 1.55%], p = 0.50), body weight (109.7 ± 27.7 kg vs. 114.0 ± 24.8 kg, p = 0.41) and BMI (39.3 ± 10.12 kg/m^2 vs. 40.0 ± 7.8 kg/m^2, p = 0.68) were similar between groups.

The most common comorbidities in both groups were hypertension (70 vs. 60%, oral vs. subcutaneous, p = 0.30) and hyperlipidaemia (64 vs. 74%, p = 0.28). Metformin was the most commonly prescribed glucose-lowering medication at baseline (81 vs. 82%, oral vs. subcutaneous, p = 0.91), and a large proportion of the cohort had been prescribed sulfonylureas (SUs) (62 vs. 44%, p = 0.06) and sodium-glucose co-transporter-2 inhibitors (SGLT2is) (64 vs. 60%, p = 0.66).

In the oral semaglutide group, among those who did not discontinue (n = 43), 35/43 individuals (81%) were escalated to the maximum dose of 14 mg, 7/43 (16%) were maintained on 7 mg, and one (2%) remained at the starting dose of 3 mg. In the subcutaneous semaglutide group, among those who did not discontinue (n = 45), 44/45 individuals (98%) were escalated to the maximum dose of 1.0 mg, with only one (2%) remaining at 0.5 mg.

Data on baseline characteristics are presented in Table 1.

Effectiveness of Oral and Subcutaneous Semaglutide

Statistically significant improvements from baseline were seen for both formulations in HbA_{1c} (19.3 ± 18.4 mmol/mol [– 1.77 ± 1.68%] and 20.8 ± 15.4 mmol/mol [– 1.90 ± 1.41%] for oral and subcutaneous respectively), body weight (– 9.0 ± 10.2 kg and – 7.2 ± 9.4 kg), BMI (– 3.3 ± 3.8 kg/m^2 and – 2.5 ± 3.3 kg/m^2), and total cholesterol (– 0.24 ± 0.49 mmol/l and – 0.38 ± 0.92 mmol/l), (Fig. 1, Table 2, Supplementary Table S1). For oral semaglutide, a statistically significant improvement was seen in triglycerides (– 0.69 ± 1.64 mmol/l, p = 0.02), and albumin (+ 1.14 ± 2.44 mmol/l, p = 0.01), (Table 2).

Comparison of Oral and SC Semaglutide

ETDs for change from baseline in all outcome measures were calculated. The 95% CIs for the ETDs crossed zero for all outcome measures, and hence we observed no statistically significant differences between oral and subcutaneous semaglutide in terms of change from baseline (Fig. 1, Supplementary Table S1, and Table 2). The change in total cholesterol and triglycerides showed an association with weight loss and with decreasing HbA_{1c}, but these were not statistically significant.

Table 1 Baseline characteristics

	All patients ($n = 103$)	Oral semaglutide ($n = 53$)	Subcutaneous semaglutide ($n = 50$)	p value
Demographics				
Age, years	57.28 ± 10.52	58.45 ± 10.35	56.04 ± 10.67	0.25
Male, *n* (%)	49 (48)	26 (49)	23 (46)	0.76
Clinical characteristics				
HbA_{1c}, %	9.38 ± 1.41	9.28 ± 1.29	9.48 ± 1.55	0.50
HbA_{1c}, mmol/mol	79.01 ± 15.41	78.1 ± 14.10	80.2 ± 16.94	0.50
$HbA_{1c} < 9.0\%$, *n* (%)	50 (49)	26 (49)	24 (48)	
$HbA_{1c} \geq 9.0\%$, *n* (%)	53 (51)	27 (51)	26 (52)	
BMI, kg/m^2	39.63 ± 9.05	39.28 ± 10.17	40.01 ± 7.78	0.68
BMI < 35, *n* (%)	36 (35)	19 (36)	17 (34)	
BMI ≥ 35, *n* (%)	67 (65)	34 (64)	33 (66)	
Weight, kg	111.8 ± 26.31	109.74 ± 27.74	113.99 ± 24.79	0.41
Any microvascular complication, *n* (%)	47 (46)	26 (62)	21 (42)	0.06
Retinopathy, *n* (%)	30 (29)	15 (36)	15 (30)	0.081
Neuropathy, *n* (%)	22 (21)	15 (28)	7 (14)	0.08
Microalbuminuria, *n* (%)	25 (24)	13 (25)	12 (24)	0.95
Any macrovascular complication, *n* (%)	13 (13)	6 (11)	7 (14)	0.68
PAD, *n* (%)	2 (2)	0 (0)	2 (4)	0.14
Ischemic heart disease, *n* (%)	8 (8)	3 (6)	5 (10)	0.41
Stroke, *n* (%)	8 (8)	4 (8)	4 (8)	0.93
HF, *n* (%)	7 (7)	3 (6)	4 (8)	0.64
Hypertension, *n* (%)	67 (65)	37 (70)	30 (60)	0.30
Hyperlipidaemia, *n* (%)	71 (69)	34 (64)	37 (74)	0.28
Medications				
Metformin, *n* (%)	84 (82)	43 (81)	41 (82)	0.91
SU, *n* (%)	55 (53)	33 (62)	22 (44)	0.06
SGLT2i, *n* (%)	64 (62)	34 (64)	30 (60)	0.66
Insulin, *n* (%)	23 (22)	10 (19)	13 (26)	0.39
Statin, *n* (%)	80 (78)	44 (83)	36 (72)	0.18
ACE/ARB, *n* (%)	62 (60)	35 (66)	27 (54)	0.21
Aspirin, *n* (%)	22 (21)	12 (23)	10 (20)	0.74

Table 1 continued

	All patients ($n = 103$)	Oral semaglutide ($n = 53$)	Subcutaneous semaglutide ($n = 50$)	p value
Semaglutide dosing	($n = 96$)	($n = 46$)	($n = 50$)	
Oral 3 mg	2 (4)	2 (4)		
Oral 7 mg	8 (17)	8 (17)	–	–
Oral 14 mg	36 (78)	36 (78)	–	–
Subcutaneous 0.5 mg	1 (2)	–	1 (2)	–
Subcutaneous 1 mg	49 (98)	–	49 (98)	–

Values presented as mean ± SD where appropriate

ACE/ARB angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, *BDR* background diabetic retinopathy, *BMI* body mass index, *HbA_{1c}* glycated haemoglobin, *HF* heart failure, *MDR* moderate diabetic retinopathy, *PAD* peripheral arterial disease, *PDR* proliferative diabetic retinopathy, *PPDR* pre-proliferative diabetic retinopathy, *SD* standard deviation, *SGLT2i* sodium/glucose cotransporter-2 inhibitor, *SU* sulfonylurea

Subgroup Analysis

HbA_{1c} Subgroups

Statistically significant changes from baseline were seen in HbA_{1c}, BMI, and body weight across HbA_{1c} subgroups for both formulations of semaglutide (Fig. 2A–C, Supplementary Table S2). For both formulations, improvement in HbA_{1c} was significantly greater for the group with $HbA_{1c} \geq 75$ mmol/mol (9.0%) at baseline versus $HbA_{1c} < 75$ mmol/mol (9.0%) at baseline (Oral: −11.5 mmol/mol [−1.05%] vs. −27.3 mmol/mol [−2.50%] for low and high baseline HbA_{1c} respectively, $p < 0.001$; Subcutaneous: −15.6 mmol/mol [−1.43%] vs. −25.7 mmol/mol [−2.35%], $p < 0.01$).

BMI Subgroups

Statistically significant changes from baseline were seen in HbA_{1c}, BMI, and body weight across BMI subgroups for both formulations (Fig. 2D–F, Supplementary Table S2). For oral semaglutide, improvement in BMI and body weight was numerically greater in group with BMI ≥ 35 kg/m^2 at baseline versus BMI < 35 kg/m^2 at baseline, although the difference did not reach statistical significance.

Age Subgroups

Statistically significant changes from baseline were seen in HbA_{1c}, BMI, and body weight across age subgroups for both formulations of semaglutide (Fig. 2G–I, Supplementary Table S2), the improvements seen were similar across age groups.

Safety

AE profiles of oral and subcutaneous semaglutide were similar, and comparable with expectations for the GLP-1 RA class. The commonest AE in both groups was nausea and vomiting, recorded for 21 individuals in each group. There were no significant differences in the number of individuals experiencing GI side effects (both upper and lower) between treatment groups (Supplementary Table S3).

Five individuals taking subcutaneous semaglutide (10%) discontinued treatment (all on 1 mg semaglutide), with one switching to the oral formulation, two switching to alternative weekly GLP-1 RAs, and two requiring insulin. In the oral semaglutide group, one individual temporarily stopped treatment, and nine (17%) permanently discontinued. Of these, one was on 3 mg semaglutide, one was on 7 mg, one was on 14 mg, and the remainder had no dose recorded.

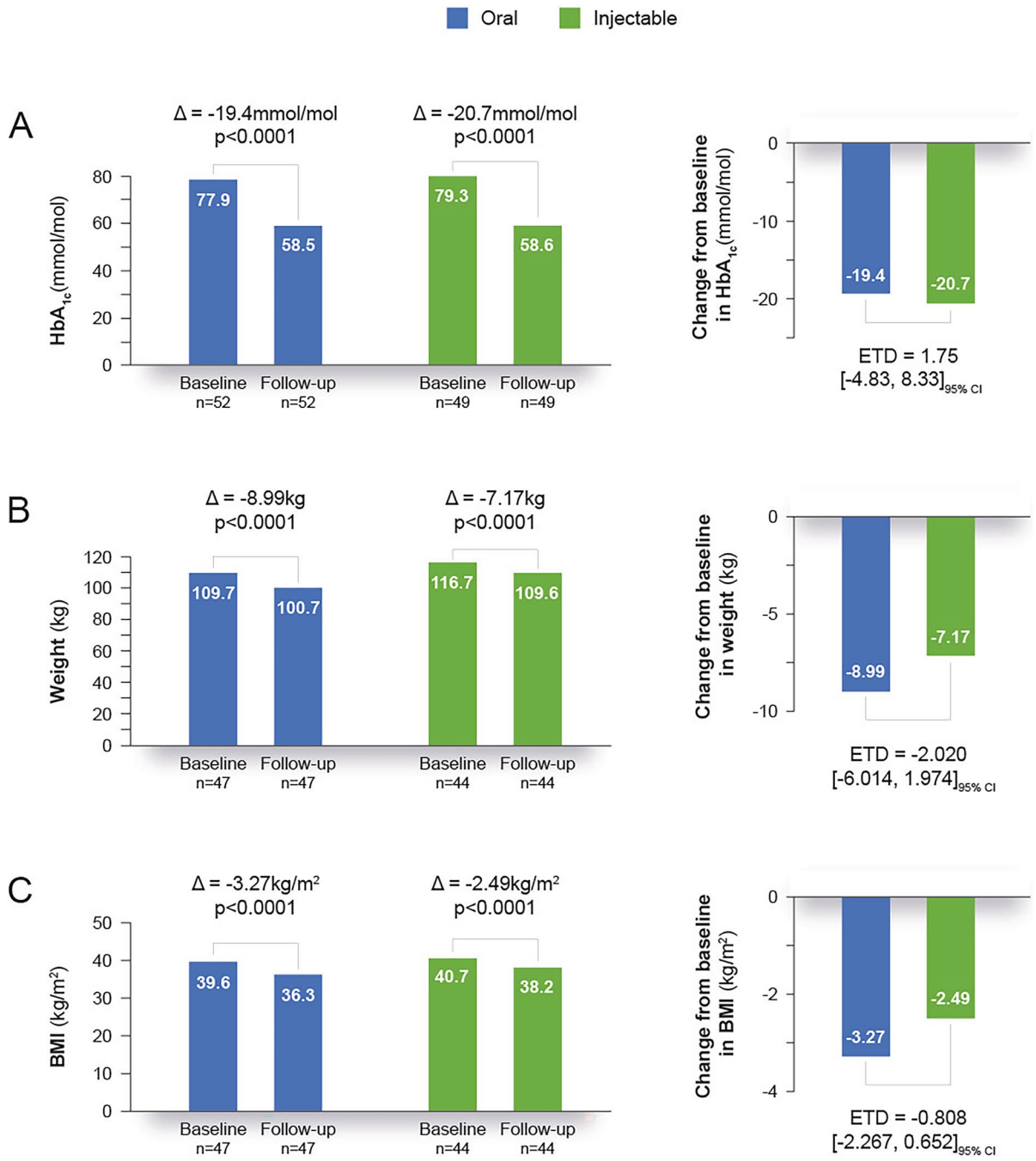

Fig. 1 Values at baseline and follow-up; change from baseline for **A** HbA_{1c}, **B** weight and **C** BMI. *BMI* body mass index, *CI* confidence interval, *ETD* estimated treatment difference, *HbA_{1c}* glycated haemoglobin

DISCUSSION

The current study is the first to evaluate the use of both oral and subcutaneous semaglutide in the same real-world clinical practice.

People initiating semaglutide in this secondary care clinic had poor glycaemic control. Mean HbA_{1c} for the cohort was

Table 2 Clinical outcomes: metabolic, liver and kidney parameters

	Oral semaglutide					Subcutaneous semaglutide					ETD (oral vs. sub.) [95% CI]
	N	Baseline	Follow-up	CFB	*p* value	*N*	Baseline	Follow-up	CFB	*p* value	
Total cholesterol, mmol/l	32	4.02 ± 1.08	3.78 ± 0.93	− 0.24 ± 0.49	**0.01**	37	4.52 ± 1.29	4.14 ± 1.13	− 0.38 ± 0.92	**0.02**	0.0800 [− 0.267, 0.427]
Triglycerides, mmol/l	32	2.71 ± 2.12	2.01 ± 1.13	− 0.69 ± 1.64	**0.02**	37	2.81 ± 1.47	2.38 ± 2.42	− 0.44 ± 1.68	0.12	− 0.202 [− 0.940, 0.536]
HDL, mmol/l	32	1.14 ± 0.27	1.18 ± 0.31	0.04 ± 0.14	0.14	37	1.11 ± 0.32	1.11 ± 0.24	0.00 ± 0.23	0.94	0.0282 [− 0.0606, 0.117]
LDL, mmol/l	30	1.78 ± 0.88	1.74 ± 0.72	− 0.05 ± 0.41	0.54	34	2.27 ± 1.21	2.16 ± 1.05	− 0.11 ± 0.89	0.46	0.0166 [− 0.319, 0.352]
Bilirubin, mmol/l	34	8.18 ± 4.65	8.44 ± 4.45	0.26 ± 2.90	0.60	41	8.24 ± 6.49	7.07 ± 3.84	− 1.17 ± 3.96	0.07	1.431 [− 0.111, 2.973]
ALP, mmol/l	35	93.29 ± 30.16	91.71 ± 26.67	− 1.57 ± 18.02	0.61	42	92.76 ± 35.03	94.52 ± 36.98	1.76 ± 19.00	0.55	− 3.896 [− 12.02, 4.226]
ALT, mmol/l	35	36.66 ± 34.98	31.49 ± 21.24	− 5.17 ± 25.31	0.24	42	26.14 ± 12.56	23.52 ± 10.88	− 2.62 ± 12.48	0.18	− 1.765 [− 9.903, 6.372]
Albumin, mmol/l	35	43.66 ± 2.74	44.80 ± 2.86	1.14 ± 2.44	**0.01**	42	43.00 ± 2.65	43.81 ± 4.16	0.81 ± 3.90	0.19	0.506 [− 0.927, 1.938]
eGFR, ml/min/1.73 m^2	50	77.58 ± 15.27	76.96 ± 15.32	− 0.62 ± 6.32	0.49	31	64.77 ± 15.51	65.58 ± 15.70	0.81 ± 6.54	0.50	− 1.372 [− 4.201, 1.458]

Values given as mean ± SD where appropriate. Bold text indicates statistical significance

ALP alkaline phosphatase, *ALT* alanine transaminase, *BMI* body mass index, *CFB* change from baseline, *CI* confidence interval, *eGFR* estimated glomerular filtration rate, *ETD* estimated treatment difference, HbA_{1c} glycated haemoglobin, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *SD* standard deviation

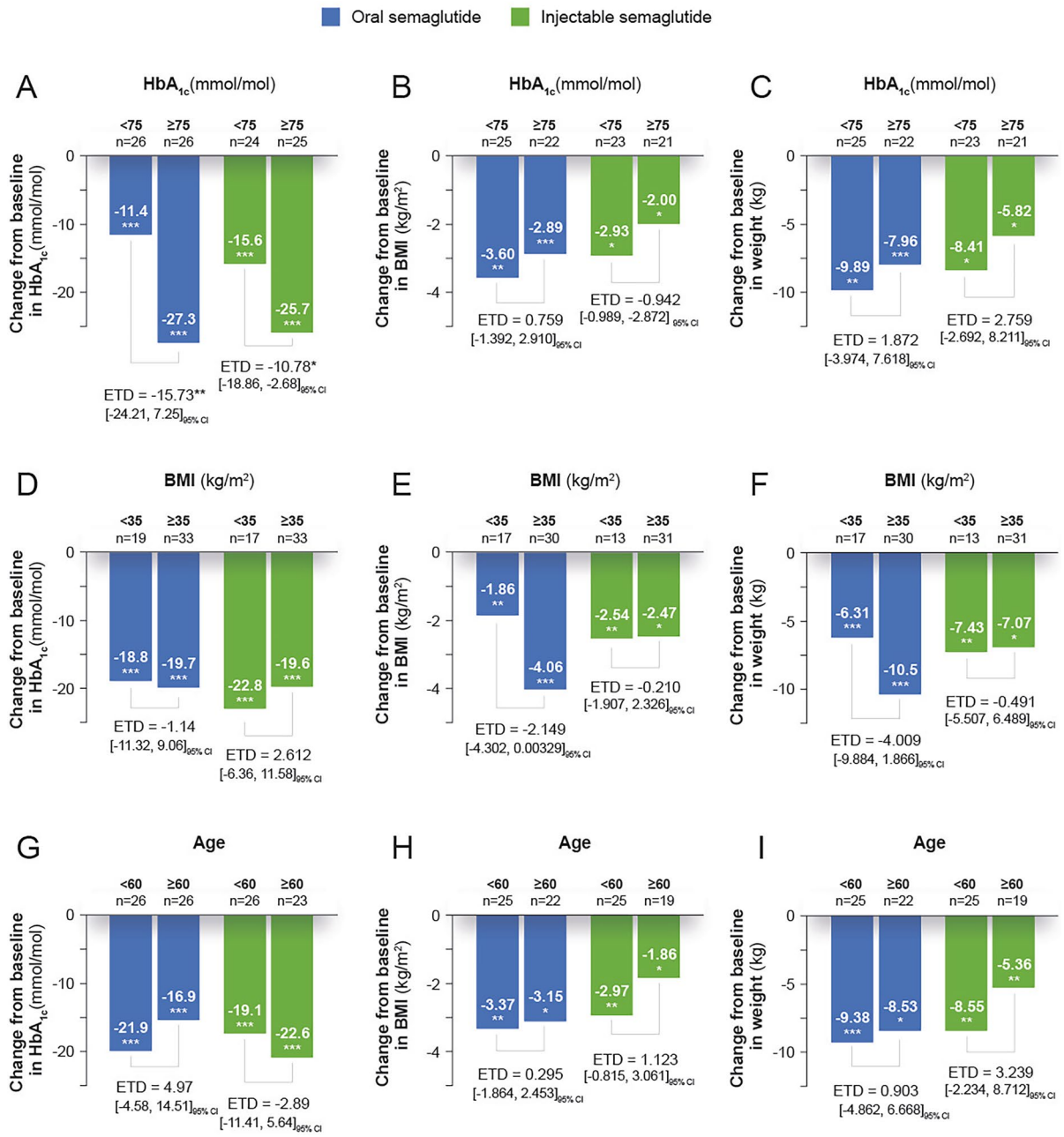

Fig. 2 Change from baseline in HbA_{1c}, BMI and weight, stratified by **A–C** HbA_{1c}, **D–F** BMI, and **G–I** age. $^{*}p < 0.01$, $^{**}p < 0.001$, $^{***}p < 0.0001$. *BMI* body mass index, *CI* confidence interval, *ETD* estimated treatment difference, *HbA_{1c}* glycated haemoglobin

79.0 mmol/mol (9.38%); more than 40% of the cohort presented with HbA_{1c} between 64–75 mmol/mol (8.0–9.0%), and just over half had $HbA_{1c} \geq 75$ mmol/mol (9.0%), which is the threshold at which NICE recommends consideration of insulin therapy [6]. The cohort also had a high mean BMI (39.6 kg/m^2), with 65% having obesity (BMI ≥ 35 kg/m^2), in line with NICE recommendations for the initiation of GLP-1 RAs [6]. A large proportion of

the cohort were prescribed SGLT2is (62%). In line with NICE recommendations to consider SGLT2is in people with established CVD or CVD risk [6], the cohort had a high prevalence of hypertension (65%), hyperlipidaemia (69%), and obesity (65%). Additionally, 53% of participants were on SUs.

HbA_{1c} levels well above target may be indicative of therapeutic inertia. A recent study investigating the degree of therapeutic inertia associated with the prescription of GLP-1 RAs in primary care in the UK found that 54.9% of people with diabetes had an HbA_{1c} level of ≥ 75 mmol/mol (9.0%) at first prescription of subcutaneous semaglutide, which is in keeping with baseline characteristics of our cohort [23]. Additionally, a considerable proportion of our cohort (15 [30%] and 19 [36%] in the subcutaneous and oral groups respectively) were already on three oral anti-diabetes drugs (OADs).

The study period fell in the middle of the COVID-19 pandemic, where there was a minimum 6-month delay between presenting in primary care, receiving an evaluation and referral to secondary care. This may have contributed to individuals presenting at a relatively late stage in their disease course. Further, the relatively sedentary lifestyles adopted during the pandemic may have led to weight gain and worsening glycaemic control in the T2D population [24].

Both formulations of semaglutide were associated with clinically and statistically significant improvements in HbA_{1c} (− 19.3 mmol/mol [− 1.77%] and − 20.8 mmol/mol [− 1.90%] for oral and subcutaneous respectively), BMI (− 3.27 kg/m^2 and − 2.49 kg/m^2), and body weight (− 8.99 kg and − 7.17 kg). Hence, both are effective options in the real-world treatment of T2D. Additionally, as the 95% CIs crossed zero in all treatment comparisons, we observed no statistically significant differences between the two formulations of semaglutide in this real-world cohort.

Subgroup analysis showed that both formulations of semaglutide were effective in reducing HbA_{1c}, BMI and body weight across all baseline subgroups, highlighting the benefit of semaglutide across the spectrum of HbA_{1c}, weight, and age. In accordance with two other real-world studies investigating the use of semaglutide in clinical practice, significantly greater reductions in HbA_{1c} were seen in the subgroup with higher baseline HbA_{1c} [13, 14]. Additionally, in the oral semaglutide group, there was a trend towards greater reductions in body weight and BMI in the subgroup with higher baseline BMI; however, the difference did not reach statistical significance. When interpreting these results, it should be noted that these trends are expected due to the tendency of extreme values to regress to the mean upon repeated measurement.

The pivotal PIONEER and SUSTAIN clinical trial programs demonstrated the efficacy of oral and subcutaneous semaglutide across different populations, compared with placebo or other glucose-lowering medications. In the PIONEER studies 1–8, oral semaglutide was associated with a decrease in HbA_{1c} of 10.9–15.3 mmol/mol (1.0–1.4%) and a decrease in body weight of 1.6–4.4 kg; in SUSTAIN 1–10, subcutaneous semaglutide was associated with a decrease in HbA_{1c} of 13.1–19.6 mmol/mol (1.2–1.8%) and a decrease in body weight of 4.5–6.5 kg [9, 21]. In these pivotal clinical trials, the HbA_{1c} and weight reductions were smaller than those observed in our real-world study; this may be explained by a difference in baseline characteristics. In PIONEER 1–8, the baseline HbA_{1c} ranged from 64.0–67.3 mmol/mol (8.0–8.3%), and the baseline body weight from 85.9–94.0 kg, compared with 78.0 mmol/mol (9.28%) and 109.7 kg in the oral semaglutide arm of our study [9]. In SUSTAIN 1–10, this was 64.0–68.4 mmol/mol (8.0–8.4%) and 89.5–96.9 kg, compared with 80.2 mmol/mol (9.48%) and 114.0 kg in the subcutaneous semaglutide arm of our study [21].

The IGNITE study is, at time of writing, the only published study that investigates the real-world use of oral semaglutide in the UK. This study reported a mean reduction in HbA_{1c} of − 9.8 mmol/mol (− 0.9%) after 6 months [14]. This is a smaller reduction than that observed in our study; however, the baseline HbA_{1c} in IGNITE was 68.4 mmol/mol (8.4%), considerably lower than baseline HbA_{1c} in the oral semaglutide group in our study.

Semaglutide was well tolerated by most people, although approximately half in each treatment group reported GI side effects (Supplementary Table S3). A literature review found

that GI side effects can be expected in 40–70% of people taking GLP-1 RAs, but that they are mostly transitory and can be expected to resolve after the maintenance dose is reached. To improve patient experience and adherence, people initiating GLP-1 RAs should be educated on the nature of potential gastrointestinal (GI) side effects and strategies to mitigate them (e.g., following dietary recommendations). Healthcare providers may also slow or halt dose escalation in response to emerging side effects [22].

This was a retrospective study using prescription-based data, and hence presence of missing values for some variables is an intrinsic limitation. There was no comparator arm, meaning that other explanations for observed changes in variables (e.g. HbA_{1c}) cannot be ruled out, and this study cannot be used to position semaglutide relative to relevant comparators in the clinical pathway. As this study represented a single-centre experience, the sample size is small, which should be considered when interpreting the results. The follow-up period of 6 months is relatively short and limits conclusions about persistence and treatment duration. Data regarding adherence and persistence may not have been fully captured in medical records. Although covariables were not included in the linear mixed models, a random intercept term was included to account for individual differences in baseline values.

Strengths of the study include the fact that all individuals initiated on semaglutide attended four routine follow-up visits, and data on HbA_{1c} were available at baseline and follow-up for all but one person in each group. This may make the study less subject to follow-up bias, in that the availability of follow-up data is not indicative of disease severity.

Whilst there is scope for a longer-term follow-up, useful insights were gained from this study, with potential benefit for future clinical practice. The documented comparable effectiveness of the oral and subcutaneous formulations supports offering people the choice of the two formulations with an informed discussion prior to prescribing.

CONCLUSIONS

Both formulations of semaglutide provide clinically relevant and statistically significant improvement in HbA_{1c}, BMI and body weight from baseline in real-world clinical practice. In our real-world cohort, we observed no statistically significant between treatment differences for these key outcomes; however the oral formulation may be easier to initiate in some clinical settings such as primary care, which may grant faster access to treatment, and potentially save costs.

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Declarations

Conflict of Interest. Sharmistha Roy Chowdhury reports receiving payment for lectures, presentations and/or educational activities from Novo Nordisk, AstraZeneca, Boehringer Ingelheim and Eli Lilly and Company, and support for attending meetings from Novo Nordisk. Stephen C. Bain reports grants and personal fees from AstraZeneca, Novo Nordisk and Sanofi-Aventis; personal fees from Boehringer Ingelheim, Eli Lilly and Merck Sharp & Dohme; grants from Medscape; expert advice provided to All-Wales Medicines Strategy Group and National Institute for Health and Care Excellence UK. In addition, Stephen C. Bain is an Editorial Board member of Diabetes Therapy. Stephen C. Bain was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Fethi Sadouki and Edward Collins are employees of Novo Nordisk Ltd. Frederick Keen, Ridhi Bhagi, Yuan S. J. Lim, and Silviu L. Cozma have nothing to disclose. Since this manuscript was written, the following authors have changed affiliation: Sharmistha Roy Chowdhury is now affiliated with the University Hospital of Wales, Cardiff and Vale UHB, Cardiff, United Kingdom. Frederick Keen is now affiliated with University Hospital Llandough, Cardiff and Vale UHB, Cardiff, United Kingdom. Yuan Shen Justin Lim is now affiliated with Ipswich Hospital, East Suffolk and North Essex Foundation Trust, Ipswich, United Kingdom.

Ethical Approval. This study was assessed using the decision tool on the HRA website [http://www.hra-decisiontools.org.uk/research/]. Ethics committee approval was not required, as the analysis was conducted as part of a service-based evaluation project to examine the effects of semaglutide therapy, which is routine in our local practice. Only de-identified secondary data were used. Approval from the head of department was received.

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