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BRIEF REPORT

Real-World Clinical Experience of Oral Semaglutide in a Secondary Diabetes Clinic in the UK: A Retrospective Observational Study

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ABSTRACT

***Introduction*:** Oral semaglutide improves cardiovascular risk factors in people with type 2 diabetes (T2D) in clinical trials, though real-world evidence is limited. We aimed to determine the real-world impact of oral semaglutide on routinely collected clinical data in our practice.
***Methods*:** People with T2D initiated on oral semaglutide in secondary care diabetes clinics at two hospital sites in Wales (United Kingdom) were included. Data were collected on reasons for oral semaglutide initiation and changes in bodyweight, blood pressure, glycemic control, and lipid profiles over follow-up at 3–6 months, and at 6–12 months. Data were collected to determine the safety of oral semaglutide.
***Results*:** Seventy-six patients were included, with a median age 59.3 [51.4–67.6] years, and 38 (50.0%) patients were female. The most common reasons for oral semaglutide were need for weight loss and improved glycemia (69.8%), and improved glycemia alone (25.0%). Oral semaglutide associated with significantly reduced bodyweight (– 3.3 kg), body mass index (BMI) (– 0.9 kg/m^2), glycated hemoglobin (HbA1c) (– 11 mmol/mol), and total cholesterol (– 0.4 mmol/l) by 3–6 months follow-up. At 6–12 months, there was a significant reduction in systolic blood pressure (– 7.0 mmHg), in addition to sustained reductions in other metabolic parameters. By 12 months, 18 (23.6%) patients had discontinued the drug, largely resulting from gastrointestinal disturbance, but there were no serious events in this cohort.
***Conclusions*:** Oral semaglutide was effective in improving cardiovascular risk factors in this real-world population living with T2D, and no serious events were identified related to oral semaglutide in this patient group.

Keywords: Semaglutide; Glucagon-like peptide-1 receptor analogues; GLP-1; Type 2 diabetes; Weight loss; Real world

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Key Summary Points
This is a real-world study of patients with type 2 diabetes prescribed oral semaglutide.
Oral semaglutide improved bodyweight, glycated hemoglobin, and lipids at 3–6 and 6–12 months.
Patients often reported gastrointestinal disturbance, and 23.7% stopped semaglutide within 1 year.
There were no serious adverse events attributable to the drug over follow-up.

INTRODUCTION

Clinical interest in therapies for people with type 2 diabetes (T2D) has prospered in the last decade with many demonstrating a major impact beyond glycemic control. In clinical trials, at least, glucagon-like peptide-1 receptor analogues (GLP-1RAs) reduce 3-point major adverse cardiovascular events (3P-MACE), and progressive albuminuria amongst other benefits in people with T2D [1]. These drugs show promise in the prevention and management of stroke [2], and of course in the management of people living with obesity [3, 4]. These observations have transformed the management of people with T2D, with a focus on preventing and controlling disease-related complications. This has triggered a surge in GLP-1RA use, contributing to the recent global shortage of these medicines [5].

Semaglutide was first developed for the treatment of people with T2D as a once-weekly injection (Ozempic) [6], and later as a once-daily oral preparation (Rybelsus) [7]. In trials of people with T2D, injectable semaglutide improves cardiovascular risk factors and outcomes [6], and oral semaglutide improves cardiovascular risk factors, at least [7]. The ongoing SOUL [8], and FLOW [9], studies are evaluating the cardiovascular and renal outcomes associated with oral semaglutide, respectively. In clinical trials, semaglutide is associated with nausea, diarrhea, and constipation, amongst other side effects [6, 7]. Real-world studies support the benefits of injectable semaglutide on several cardiovascular risk factors [10–13], though few reports explore oral semaglutide in people with T2D outside of the trial setting [14–17]. Given the ease of oral semaglutide administration and shortage of injectable semaglutide, the use of oral formulations is of major interest, especially in primary care. In this retrospective study, we aim to determine the real-world impact and tolerability of oral semaglutide in people with T2D.

METHODS

Subjects

All patients with T2D initiated on oral semaglutide in diabetes clinics at two secondary care sites in Wales, United Kingdom (Neath Port Talbot and Royal Glamorgan Hospital) January 2021-January 2023, aged greater than 18 years were included, with no other exclusion criteria. Electronic records, including clinic letters and test results, were reviewed retrospectively to determine reasons for oral semaglutide initiation, and changes in bodyweight, blood pressure (BP), glycemic control, lipid profiles, and liver enzymes over follow-up. Baseline data from the time of semaglutide initiation were collected and compared with clinical data collected at a follow-up clinic visit at 3–6 or 6–12 months. Data were also collected to determine the safety of oral semaglutide, including side effects and discontinuation rate.

Ethical Approval

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 following the introduction of new

diabetes therapies. Data were collected retrospectively, unidentified for the analysis, and are presented anonymously. Therefore, ethical approval was not required.

Statistical Analysis

Statistical analysis was conducted using SPSS (version 29). Categorical data are presented by number (%) and continuous data following a non-parametric distribution are presented by median [interquartile range]. The statistical significance of changes over follow-up are determined using Wilcoxon signed-rank test. Statistical significance is defined as $p < 0.05$.

RESULTS

Participant Characteristics

Seventy-six participants were identified and included in this analysis. At initiation, patients had a median age 59.3 [51.4–67.6] years, T2D duration 13.0 [8.5–19.0] years, bodyweight of 98.2 [85.1–110.1] kg, BMI 34.6 [30.7–37.6] kg/m^2, and 38 (50.0%) patients were female. Their characteristics are further presented in Table 1. Pharmacotherapies for T2D prescribed prior to semaglutide are presented in Fig. 1.

Reasons for choosing oral semaglutide were a need for weight loss and improved glycemia ($n = 53$, 69.8%), improved glycemia alone ($n = 19$, 25.0%), weight loss alone ($n = 2$, 2.6%), steatotic liver disease ($n = 1$, 1.3%), and high cardiovascular risk ($n = 1$, 1.3%). Six (7.9%) patients were initiated due to concerns around the effect of insulin on their job, and five (6.6%) switched from injectable GLP-1RAs due to needle phobia, or supply issues.

Changes Over Follow-Up

Changes in characteristics from baseline to 3–6 months, or 6–12 months follow-up are shown in Table 2 for those in whom paired data were available. Over 3–6 months, there were significant reductions in bodyweight, body mass index (BMI), glycated hemoglobin (HbA1c), total cholesterol, and triglycerides. Over 6–12 months, there were reductions in bodyweight, BMI, systolic BP, HbA1c, and total cholesterol.

Table 1 Characteristics of people with T2D initiated on oral semaglutide

Variable	Total cohort [$n = 76$]
Age (years)	59.3 [51.4–67.6]
Weight (kg)	98.2 [85.1–110.1]
BMI (kg/m^2)	34.6 [30.7–37.6]
SBP (mmHg)	140.0 [129.0–152.0]
DBP (mmHg)	80.0 [74.0–87.0]
HbA1c (mmol/mol)	77.0 [68.0–91.0]
TC (mmol/l)	4.2 [3.7–5.0]
Triglyceride (mmol/l)	2.1 [1.5–3.0]
HDL-C (mmol/l)	1.1 [1.0–1.4]
ALT (IU/l)	23.5 [16.3–34.0]
Creatinine (μmol/l)	73.0 [63.0–86.0]

The baseline characteristics of patients included in this study

ALT alanine transaminase, *BMI* body mass index, *DBP* diastolic blood pressure, *HbA1c* glycated hemoglobin, *HDL-C* high-density lipoprotein cholesterol, *SBP* systolic blood pressure, *T2D* type 2 diabetes, *TC* total cholesterol

Adverse Events and Safety

Within 6 months of starting semaglutide, 24 (31.6%) patients reported adverse effects [nausea, $n = 16$; diarrhea, $n = 4$; constipation, $n = 2$; abdominal pain, $n = 1$; hypoglycemia, $n = 1$] and 14 (18.4%) discontinued semaglutide. By 12 months of follow-up, an additional five patients reported drug-related effects [nausea, $n = 4$; hypoglycemia, $n = 1$] and four of these discontinued semaglutide. There was one

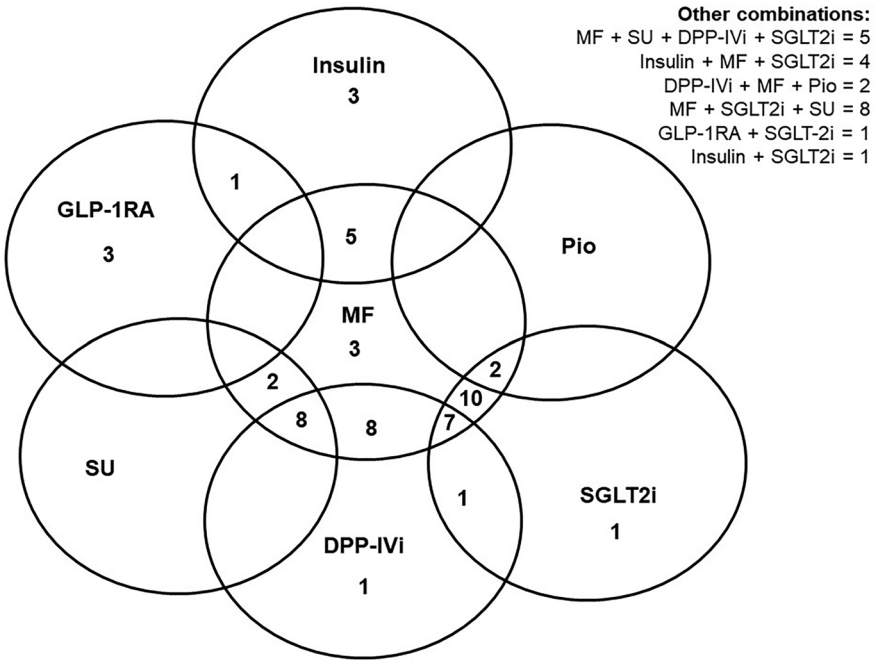

Fig. 1 Summary of the medicines prescribed to patients included prior to initiation of oral semaglutide. *DPP-IVi* dipeptidyl peptidase-4 inhibitor, *GLP-1RA* glucagon-like peptide-1 receptor analogues, *MF* metformin, *Pio* pioglitazone, *SGLT-2i* sodium-glucose co-transporter-2 inhibitor, *SU* sulphonylurea

observed death, for which we are not able to ascertain the cause, but there were no hospitalizations resulting from adverse events. Of those who developed hypoglycemia, one was prescribed insulin only, and the other metformin, gliclazide, and dapagliflozin. Of 42 patients with dose-related data at 6–12 months, 3 (7.1%) were prescribed 3 mg, 16 (38.1%) prescribed 7 mg, and 23 (54.8%) prescribed 14 mg.

DISCUSSION

In this evaluation, we aimed to determine the impact of oral semaglutide on routinely collected clinical data in people with T2D in our practice. We observed clinically significant median HbA1c reductions of 11 mmol/mol [1.0%] and 16 mmol/mol [1.5%] at 3–6 and 6–12 months, respectively. We also observed reductions in bodyweight, BMI, and total cholesterol at 3–6 and 6–12 months and significant reductions in triglycerides at 3–6 months, and systolic BP at 6–12 months. Compared with clinical trials of oral semaglutide, these data are largely comparable. The PIONEER-6 study reported that oral semaglutide 14 mg was associated with a mean HbA1c reduction of 11 mmol/mol, bodyweight reduction 4.2 kg (4.6% baseline), and systolic BP reduction of 5.0 mmHg over 15.9 months, compared to our cohort with median reductions of 16 mmol/mol, 7.0 kg (6.6% baseline), and 7.0 mmHg over 6–12 months, respectively [7]. Likewise, previous real-world studies have shown HbA1c reductions of 3-10 mmol/mol, body weight 2.0–4.4 kg, and systolic BP 12.5 mmHg [14–17]. The consistency of our data with previous trials, and albeit limited real-world comparisons, support the favorable impact of oral semaglutide in people living with T2D. Though interestingly in this cohort, these changes were achieved with only 54.8% of the patients included reaching the maximum 14-mg dose or oral semaglutide by 6–12 months follow-up. This may be due to several reasons, including treatment inertia with respect to dose titration,

Table 2 Participant characteristics over follow-up

Variable	Baseline	Follow up	Significance
3–6 months			
Weight (kg) [*n* = 24]	88.6 [78.3–108.2]	85.3 [74.5–106.1]	< 0.001
BMI (kg/m^2) [*n* = 24]	34.0 [29.9–36.5]	33.1 [28.3–35.1]	< 0.001
SBP (mmHg) [*n* = 22]	142.0 [129.5–156.5]	139.5 [127.0–156.0]	NS
DBP (mmHg) [*n* = 22]	79.5 [74.0–86.3]	79.5 [77.5–88.3]	NS
HbA1c (mmol/mol) [*n* = 35]	79.0 [72.0–91.0]	68.0 [55.0–74.0]	< 0.001
TC (mmol/l) [*n* = 28]	4.3 [3.7–4.8]	3.9 [3.2–4.7]	< 0.01
Triglyceride (mmol/l) [*n* = 27]	2.0 [1.6–2.8]	1.9 [1.5–2.8]	< 0.05
HDL-C (mmol/l) [*n* = 28]	1.1 [1.0–1.3]	1.1 [1.0–1.2]	NS
ALT (IU/L) [*n* = 27]	19.0 [12.0–35.0]	19.0 [13.0–25.0]	NS
Creatinine (μmol/l) [*n* = 36]	70.0 [57.5 -88.0]	71.0 [56.3–85.5]	NS
6–12 months			
Weight (kg) [*n* = 29]	106.3 [88.5–116.2]	99.3 [83.9–109.5]	< 0.001
BMI (kg/m^2) [*n* = 29]	36.4 [32.4–42.0]	34.0 [29.5–40.9]	< 0.001
SBP (mmHg) [*n* = 26]	141.0 [128.0–150.3]	134.0 [124.3–140.8]	< 0.05
DBP (mmHg) [*n* = 26]	79.0 [72.8–84.3]	79.5 [67.5–86.3]	NS
HbA1c (mmol/mol) [*n* = 33]	77.0 [67.5–91.0]	61.0 [56.0–82.5]	< 0.001
TC (mmol/l) [*n* = 30]	4.2 [3.6–4.8]	3.8 [3.5–4.2]	< 0.01
Triglyceride (mmol/l) [*n* = 30]	2.3 [1.3–3.3]	1.9 [1.4–2.7]	NS
HDL-C (mmol/l) [*n* = 30]	1.1 [1.0–1.3]	1.1 [1.0–1.3]	NS
ALT (IU/L) [*n* = 22]	24.0 [14.0–34.0]	22.0 [15.0–27.0]	NS
Creatinine (μmol/l) [*n* = 32]	79.0 [61.0–92.8]	81.5 [62.3–98.5]	NS

Paired changes observed over follow-up from baseline at 3–6 months, or 6–12 months. The number of patients with paired data at either 3–6 or 6–12 months is indicated by "*n* = " in the appropriate row. Patient follow-up may have occurred at either a 3–6- or 6–12-month interval following initiation of oral semaglutide, and paired results do not necessarily represent the same patients in both time frames

ALT alanine transaminase, *BMI* body mass index, *DBP* diastolic blood pressure, *HbA1c* glycated hemoglobin, *HDL-C* high-density lipoprotein cholesterol, *SBP* systolic blood pressure, *TC* total cholesterol

a prolonged dose-escalation phase, or patients declining further dose increases associated with adverse events, for example.

We observed that 18 (23.7%) patients discontinued semaglutide within 12 months, and 29 (38.2%) patients reported adverse effects of semaglutide, which were largely gastrointestinal in nature. In PIONEER-6, 184/1591 (11.6%) patients discontinued semaglutide [7], around 50% less than in this real-world study. This may reflect the greater motivation of trial participants to continue with trial-related interventions or other differences. Of course, given our relatively small

cohort, conclusions are limited. Nonetheless, there were no hospitalizations or other serious adverse events (including no cases of reported worsening retinopathy) associated with semaglutide use identified in this cohort. While hypoglycemia is not typically associated with semaglutide, two (2.6%) patients reported this, but both may be explained by other prescribed agents (gliclazide, insulin).

Considering the relative global shortage of injectable semaglutide, comparative studies exploring the differential impact of injectable and oral semaglutide are of major interest. A recently published real-world retrospective study comparing oral injectable semaglutide at a single UK center found no statistically significant difference in glycemic or bodyweight changes between the groups [18]. Likewise, a recently published multicenter observational study observed a similar change in body weight between people prescribed oral (−3.3 kg) and injectable (−3.7 kg) semaglutide over 18 months, with similar changes in HbA1c noted between the groups also [19]. A previous systematic review and meta-analysis comparing oral versus injectable semaglutide as an add-on therapy to basal insulin observed that oral semaglutide was at least as effective as injectable therapy [20]. Given these observations, we await the SOUL cardiovascular trial outcome [8] with great interest, as current evidence would suggest a beneficial impact on cardiovascular outcomes, though this is currently unknown.

Implications for Practice

This work highlights some important implications for practice associated with the use of oral semaglutide in people with T2D. Given the relative ease of administering oral versus injectable semaglutide, it may support earlier use of GLP-1RA therapy in people with T2D. Indeed, the initiation of GLP-1RA therapy in real practice is often delayed due to patient concerns around self-injection, or the clinician's belief that oral therapies are preferred by patients, or a lack of time and resources to educate patients on injection administration, devices, and dosing schedules. Therefore, oral GLP-1RAs help to overcome the clinical inertia associated with initiating the injectable GLP-1RAs. Naturally, this could reduce healthcare burden, with less patients requiring referral to secondary care services owing to improved glycemia and improved cardiovascular risk factors. Of course, the ongoing SOUL trial [8] is currently investigating the impact of oral semaglutide on cardiovascular outcomes.

Limitations

This study is limited by patient numbers, a lack of control group, and the biases which affect retrospective studies. There were missing follow-up data, with some having follow-up at 3–6 months, and others at 6–12 months only. This, along with unreliable information regarding smoking status, also limited calculation of the change in atherosclerotic cardiovascular disease (ASCVD) risk with semaglutide use. Given inclusion of all patients prescribed oral semaglutide at the two sites, patients with heart failure or who were prescribed medications which affect weight (e.g., steroids) were included, which may confound results. Given all the patients included in this retrospective observational study received semaglutide, there is no comparison group. Given prescribing restrictions in pregnancy, none of the subjects were pregnant in the study period. There was limited information available in this retrospective study on the duration of the adverse events reported. Therefore, these findings may not be generalizable to other populations.

CONCLUSIONS

Use of oral semaglutide was associated with significantly improved bodyweight, glycemic control, and lipid profiles from 3 to 6 months, persisting to 6–12 months. Longer-term, real-world prospective studies would be useful to confirm whether the observed cardiovascular (CV) risk factor benefits extend both beyond the

clinical trial setting in people with T2D and into improved CV outcomes in this patient group.

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Author Contributions. DMW Formal analysis, Data acquisition, Writing original draft; Writing—review & editing; BAA Data acquisition, Writing—Review & Editing; AS Data acquisition, Writing—Review & Editing; GS Data acquisition, Writing—Review & Editing; SCB Conceptualization, Methodology, Writing—Review & Editing, Supervision; AK Conceptualization, Methodology, Writing—Review & Editing, Supervision; TM Conceptualization, Methodology, Writing—Review & Editing, Supervision.

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Data Availability. All data generated or analyzed during this study are included in this published article/as supplementary information files.

Declarations

Conflict of Interest. David M Williams received honoraria from AstraZeneca unrelated to this work. Stephen Bain received grants, teaching sponsorship and honoraria from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Merck Sharp & Dohme, Novo Nordisk A/S, Pfizer, Sanofi, and Takeda unrelated to this work. Stephen Bain is an Editorial Board member of Diabetes Therapy. Stephen Bain was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Thinzar Min has received honoraria from Abbott Diabetes Care, AstraZeneca, Boehringer Ingelheim, and Napp unrelated to this work. Barbara-Alex Alberts, Asem Sharaf, Giselle Sharaf, and Atul Kalhan have no competing interests to declare.

Ethical Approval. 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 following the introduction of new diabetes therapies. Data were collected retrospectively, unidentified for the analysis and are presented anonymously. Therefore, ethical approval was not required.

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