ORIGINAL RESEARCH

The Impact of Substantial Improvements in HbA1c and Weight Loss on the Medication Preferences of People with Type 2 Diabetes

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Purpose: To quantify the preferences of people with type 2 diabetes (T2D) for treatment attributes of a glucose-dependent insulinotropic polypeptide (GIP)/glucagon-like peptide-1 (GLP-1) receptor agonist (RA) versus an injectable GLP-1 RA medication profile.

Patients and Methods: Injection-naive people taking oral medications for T2D in the US and UK completed a web survey including a discrete choice experiment to quantify patients' preferences for five treatment attributes: delivery system, frequency of nausea, frequency of hypoglycemia, HbA1c reduction, and weight reduction. Attributes and levels were based on head-to-head clinical trial data of tirzepatide 5mg, 10mg, and 15mg versus semaglutide 1mg. Preference data were analyzed separately by country using multinomial mixed logit (MXL) models. MXL parameters were used to estimate the predicted preference for each tirzepatide dose versus semaglutide 1mg. Direct preferences for each dose of tirzepatide versus semaglutide 1mg were elicited.

Results: Participants (N=620) in the US (N=301) and UK (N=319) were 50.8% and 50.5% female with mean ages of 60.7 years and 58.9 years, respectively. The order and magnitude of relative attribute importance (RAI) scores differed between countries. HbA1c reduction (26.3%) had the greatest impact on US participants' preferences, and hypoglycemia (32.8%) did among UK participants. Attribute-level marginal utility results indicated preferences for greater HbA1c improvements, the single-use pre-filled pen, lower hypoglycemia, greater weight reductions, and lower frequency of nausea. Assuming the availability of only tirzepatide or semaglutide 1mg, the predicted preference for tirzepatide (5, 10, and 15mg) in the US is 95.6% (vs 4.4% for semaglutide 1mg) and in the UK was 86.3% (vs 13.7% for semaglutide 1mg).

Conclusion: HbA1c reduction, frequency of hypoglycemia, and weight reduction are key drivers of preferences among people with T2D when considering medication options. Overall, people with T2D are likely to prefer the tirzepatide over the semaglutide 1mg medication profiles.

Keywords: patient preferences, discrete choice experiment, patient perspective, incretin

Introduction

The prevalence of diabetes has been increasing worldwide for the past several decades,[1] reaching over 37 million people in the US[2] and approximately five million people in the UK.[3] Over 95% of those with diabetes are classified as having type 2 diabetes (T2D), which is closely associated with higher body mass index (BMI) and low levels of physical activity.[1]

T2D is diagnosed and monitored by testing glycated hemoglobin A1c (HbA1c), which indicates average blood sugar level over the past few months; normal concentration of glucose in the blood is reflected by HbA1c levels of less than 5.7%, 5.7% to 6.4% reflects prediabetes, and 6.5% or greater reflects T2D.[4,5] As diabetes progresses, it can lead to a variety of health complications, including cardiovascular events, neuropathy, kidney failure, and diabetic retinopathy that can result in blindness. To prevent these complications, tight glycemic control and weight management is recommended, while minimizing the risk of hypoglycemia.[6,7] First-line therapy depends on comorbidities and patient factors, but generally includes metformin and comprehensive lifestyle modification.[8]

In addition to lifestyle modifications, there are several pharmacologic approaches to glycemic management of T2D. Incretin-based treatments (for example, glucagon-like peptide-1 [GLP-1] receptor agonists[9]) offer improved glycemic control, low risk of hypoglycemia, and the potential for clinically relevant weight loss.[6] Tirzepatide, a novel glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 RA, has been approved for the treatment of T2D and is in development for chronic weight management.[10,11] Additionally, tirzepatide has been associated with greater reductions in HbA1c and weight loss compared to several other T2D medications, such as basal insulin and GLP-1 RAs.[12–14]

Semaglutide has been approved for the treatment of T2D and chronic weight management.[15,16] In a Phase 3, head-to-head study comparing three doses (5mg, 10mg, and 15mg) of tirzepatide to 1mg semaglutide,[17] all doses of tirzepatide were found to be superior to semaglutide 1mg with respect to HbA1c reduction; half of the participants who received tirzepatide 15mg achieved an HbA1c of less than 5.7%, which is considered normoglycemia (ie, normal blood glucose levels). Additionally, all three tirzepatide doses were superior to semaglutide 1mg with respect to weight loss, with participants receiving the 15mg dose of tirzepatide achieving nearly double the weight loss of those receiving the 1mg dose of semaglutide.[17] Similar to the selective GLP-1 RA class, most of the adverse events (AEs) associated with tirzepatide were gastrointestinal (GI)-related, and the majority were mild to moderate in severity. Treatment discontinuation rates due to AEs were 5.1% (tirzepatide 5mg), 7.7% (tirzepatide 10mg), 7.9% (tirzepatide 15mg), and 3.8% (injectable semaglutide 1mg). Hypoglycemia <54 mg/dL was reported in 0.6% (tirzepatide 5mg), 0.2% (tirzepatide 10mg), and 1.7% (tirzepatide 15mg) of participants in the tirzepatide-treated arms, and in 0.4% of participants in the semaglutide 1mg-treated arm.[17]

Prior research has demonstrated that achieving near normoglycemia (defined as HbA1c levels near 5.7%) is considered by the majority of people with T2D to be a paradigm shift and viewed as both meaningful and important.[18,19] Thus, the new GIP/GLP-1 RA could provide meaningful benefits for people with T2D, given both the potential for significant reductions in HbA1c and weight loss, and also the association between T2D, obesity and negative health outcomes. However, it is unknown how people with T2D value the substantial reductions in HbA1c and weight loss. Furthermore, with the recent introduction of tirzepatide, it is unknown how people with T2D would trade-off between the benefits (including HbA1c reduction and weight loss), the risks (including GI side effects and hypoglycemia), and the administration procedures associated with this new treatment compared with those of currently available T2D treatments. This study aimed to quantify the preferences of people with T2D for the treatment attributes of a GIP/GLP-1 RA (tirzepatide) versus a GLP-1 RA (semaglutide 1mg) using a discrete choice experiment (DCE).

Materials and Methods
Overall Design and Sample

This was a cross-sectional online survey that included a DCE and was conducted among people aged 18 years and older with T2D in the US and UK. The study included a pilot testing phase prior to the main online survey data collection phase, including qualitative and quantitative components.

To be eligible for all study phases, participants had to be a resident of the US or UK, at least 18 years old, report having been diagnosed with T2D by a medical doctor, currently taking at least one oral medication to treat their T2D, and naïve to injectable medications. Individuals were excluded from the study if they had type 1 or gestational diabetes or if they were employed in the pharmaceutical industry or in a position with a direct role in treating people with diabetes. Individuals with established cardiovascular disease (eg, prior stroke, heart attack, or chronic heart failure) were also excluded to align with the SURPASS-2 patient population.[17] For the qualitative pilot, individuals were also excluded if they had a cognitive disability, visual impairment, or hearing difficulty.

Participants were recruited by a panel research company specializing in health outcomes research. Invitations to participate were sent via email and social media advertisements, targeting people who had been diagnosed with T2D. Efforts were made to enroll a sample in each country composed of approximately 50% women, and 13% participants aged 18–44 years, 44% participants aged 45–64 years, and 43% participants aged >65 to match the current distribution of T2D.[2] All participants provided electronic informed consent prior to participation and were remunerated for their participation.

Survey

The online survey consisted of four sections: 1) Warm-up and Experience with T2D Questions; 2) Treatment Attributes and Levels; 3) DCE and Supplementary Questions; and 4) Sociodemographic and Clinical Form. Within the DCE, participants were asked to choose between two hypothetical treatment options (Figure 1), which were composed of varying levels of a common set of five attributes: 1) HbA1c reduction, 2) weight reduction, 3) type of delivery system, 4) frequency of nausea, and 5) frequency of hypoglycemia/low blood sugar. These attributes were selected because they are key differentiating characteristics and are consistent with relevant attributes included in previous studies of medication preferences among T2D populations.[9,20–28] The attribute levels were defined based on the results of the SURPASS-2 trial (Table 1) which was a direct head-to-head study of tirzepatide 5mg, 10mg, and 15mg versus semaglutide 1mg.[17] The attribute levels shown within each treatment profile in the DCE were systematically varied based on an experimental design algorithm.

The DCE attribute levels were the same for UK and US participants, except for blood sugar (HbA1c) and weight reduction: levels for these two attributes were based on efficacy estimands from SURPASS-2 in the UK and on treatment regimen estimands from SURPASS-2 in the US to reflect country-specific prescribing information. Additionally, HbA1c was reported only as a percent for US participants, but as a percent and mmol/mol for UK participants. Weight loss was presented in units of pounds for US participants, but the option was given to UK participants for representation in pounds, kilograms, or stones.

Prior to completing the DCE questions, participants reviewed written descriptions of the medication attributes. To illustrate the two delivery systems, participants watched two brief (approximately three minutes) videos demonstrating the use of each delivery system. These videos were developed based on the Instructions for Use (IFU) documentation for

Which of these two **once-weekly** diabetes treatment options do you prefer? (Please place a tick in one box to make your selection.)

	Option 1	Option 2
Blood Sugar (HbA1c)	**87%** reach blood sugar (HbA1c) less than 6.5% (48 mmol/mol)	**74%** reach blood sugar (HbA1c) less than 6.5% (48 mmol/mol)
Average Weight Change	**17.2 lbs** weight loss **over 9 months**	**22.7 lbs** weight loss **over 9 months**
Type of Delivery System	Multi-use dial-a-dose pen	Single-use pre-filled pen
Nausea	**22.1%** of patients experience **nausea** that is mild to moderate and resolves over time	**19.2%** of patients experience **nausea** that is mild to moderate and resolves over time
Frequency of Low Blood Sugar Event (Hypoglycemia)	**0.6%** (6 out of 1,000) experience one low blood sugar event (hypoglycemia) in the first 9 months	**0.4%** (4 out of 1,000) experience one low blood sugar event (hypoglycemia) in the first 9 months
If I had to choose one product, I would prefer:	☐	☐

Figure 1 Example DCE choice task (UK sample).
Abbreviation: HbA1c, glycated hemoglobin A1C.

Table 1 DCE Attributes and Levels

Attribute	Levels
Blood sugar (HbA1c) Efficacy estimand[e]	66% reach blood sugar (HbA1c) less than 6.5% (48 mmol/mol)[a]
	74% reach blood sugar (HbA1c) less than 6.5% (48 mmol/mol)[b]
	82% reach blood sugar (HbA1c) less than 6.5% (48 mmol/mol)[c]
	87% reach blood sugar (HbA1c) less than 6.5% (48 mmol/mol)[d]
Blood sugar (HbA1c) Treatment regimen[f]	64% reach blood sugar (HbA1c) less than 6.5% (48 mmol/mol)[a]
	69% reach blood sugar (HbA1c) less than 6.5% (48 mmol/mol)[b]
	77% reach blood sugar (HbA1c) less than 6.5% (48 mmol/mol)[c]
	80% reach blood sugar (HbA1c) less than 6.5% (48 mmol/mol)[d]
Weight reduction Efficacy estimand[e]	On average, patients experience a weight loss of [6.2 kg / 13.7 lbs.] over 9 months of treatment[a]
	On average, patients experience a weight loss of [7.8 kg / 17.2 lbs.] over 9 months of treatment[b]
	On average, patients experience a weight loss of [10.3 kg / 22.7 lbs.] over 9 months of treatment[c]
	On average, patients experience a weight loss of [12.4 kg / 27.3 lbs.] over 9 months of treatment[d]
Weight reduction Treatment regimen[f]	On average, patients experience a weight loss of 12.6 lbs. over 9 months of treatment[a]
	On average, patients experience a weight loss of 16.8 lbs. over 9 months of treatment[b]
	On average, patients experience a weight loss of 20.5 lbs. over 9 months of treatment[c]
	On average, patients experience a weight loss of 24.7 lbs. over 9 months of treatment[d]
Delivery system	Multi-use dial-a-dose pen[a,g]
	Single-use pre-filled pen[b,c,d,h]
Nausea	17.4% of patients experience nausea that is mild to moderate and resolves over time[b]
	17.9% of patients experience nausea that is mild to moderate and resolves over time[a]
	19.2% of patients experience nausea that is mild to moderate and resolves over time[c]
	22.1% of patients experience nausea that is mild to moderate and resolves over time[d]
Frequency of low blood sugar event (hypoglycemia)	0.2% (2 out of 1000) of patients experience one low blood sugar event (hypoglycemia) in the first 9 months of treatment[c]
	0.4% (4 out of 1000) of patients experience one low blood sugar event (hypoglycemia) in the first 9 months of treatment[a]
	0.6% (6 out of 1000) of patients experience one low blood sugar event (hypoglycemia) in the first 9 months of treatment[b]
	1.7% (17 out of 1000) of patients experience one low blood sugar event (hypoglycemia) in the first 9 months of treatment[d]

Notes: [a]Level associated with semaglutide 1 mg in SURPASS-2 clinical trial.[17] [b]Level associated with tirzepatide 5mg in SURPASS-2 clinical trial.[17] [c]Level associated with tirzepatide 10mg in SURPASS-2 clinical trial.[17] [d]Level associated with tirzepatide 15mg in SURPASS-2 clinical trial.[17] [e]Levels to be presented to the UK participants. [f]Levels to be presented to the US participants. [g]Novo Nordisk, 2017.[15] [h]Eli Lilly and Company, 2021.[10,11]
Abbreviation: HbA1c, glycated hemoglobin A1C.

each product.[15,29] Participants were not permitted to fast forward through the videos or to proceed to the next question without first viewing the videos, however they could replay the videos as much as they wanted to for reference during the survey. The order in which these videos were shown to each participant was randomized. The tirzepatide and semaglutide devices were anonymized and only referred to as either Product X or Product Y.

Participants completed nine experimental choice tasks that were used to estimate preferences and five non-experimental, fixed-choice tasks that were embedded within the DCE. The order of the experimental choice tasks, the order of the two hypothetical treatment options within each choice task, and the order of the attributes within each choice task was randomized between participants. Two of the non-experimental questions assessed internal validity: a repeated-choice task to test choice stability and a dominance test to assess participants' attentiveness. Within the dominance test, each attribute level presented in one option was designed to be equal or superior to each attribute level in the alternative. The other three non-experimental questions appeared after all other choice tasks and were formatted identically to the DCE questions; these were direct comparisons of the anonymized profiles for each dose of tirzepatide (5mg, 10mg, 15mg) versus the profile for semaglutide (1mg).

Pilot Study

Virtual, one-on-one qualitative pilot interviews were conducted with 11 patients with T2D in the US and 10 in the UK to assess the relevance of the attributes and levels included in the DCE, as well as the general clarity, functionality, and understandability of the web survey. Based on the feedback from the qualitative pilot participants, minor revisions were made to improve the clarity of the survey. Subsequent to the qualitative pilot, a quantitative pilot was conducted among 50 patients with T2D in the US and 50 in the UK. These participants completed the web survey, including the DCE, to ensure the functionality of the web survey and the DCE design.

Statistical Analyses

All data were analyzed separately for the US and UK samples using STATA statistical software version 15 (Timberlake Consultants, Richmond, UK). All statistical tests were two-sided, using a significance level of 0.05.

Descriptive statistics (eg, mean, median, standard deviation [SD], range for continuous variables, frequency and percentages for categorical variables) were used to characterize the sample based on sociodemographic and clinical characteristics. Additionally, descriptive statistics were used to analyze the internal validity assessments and to summarize responses to the three direct comparison questions that were used to estimate the proportion of participants preferring the profile for each dose of tirzepatide compared with the profile for semaglutide 1mg.

The preference data were analyzed using a mixed logit model (MXL), which is similar to a multinomial logit model, but relaxes the assumption that all participants have the same preferences by introducing random effects into the modelling framework. The MXL was parameterized with HbA1c, weight, and hypoglycemia linearly coded and nausea and device type dummy coded. *T*-tests were used to determine whether estimated parameters were significantly different from zero. Only data from the nine experimental choice tasks were used in the estimation of preferences. In addition, the relative attribute importance (RAI) was calculated to evaluate the importance of each attribute relative to all other attributes. RAI is calculated as the range of an attribute's marginal utility divided by the sum of all attributes' marginal utility ranges.

The predicted preference, or the proportion of participants predicted to prefer each of the medication profiles, and the associated standard errors, were calculated using the model parameter estimates and the performance characteristics of each dose of tirzepatide and semaglutide from the head-to-head trial[17] to estimate the predicted probability of preferring each medication profile based on the attributes included in the DCE.

Results
Sample

A total of 620 people with T2D (US=301; UK=319) participated in the main survey between June and August 2022. About half of the participants were female (US: n=153 [50.8%]; UK: n=161 [50.5%]), with a mean age of 60.7 years in

Table 2 Sample Sociodemographic Characteristics

Characteristic	US (N=301; 48.5%)	UK (N=319; 51.5%)
Age (in years), mean (SD) [min–max]	60.7 (12.7) [20–86]	58.9 (12.5) [19–83]
Gender (male)	148 (49.2%)	158 (49.5%)
Racial background (US)[a]		
White	270 (89.7%)	–
Black or African American	25 (8.3%)	–
Asian or Asian American	11 (3.7%)	–
American Indian or Alaska Native	11 (3.7%)	–
Native Hawaiian or other Pacific Islander	1 (0.3%)	–
Racial background (UK)[a]		
English/Welsh/Scottish/Northern Irish/British	–	296 (92.8%)
White and Black Caribbean	–	19 (6.0%)
White and Asian	–	7 (2.2%)
Irish	–	4 (1.3%)
Indian	–	4 (1.3%)
Black British	–	3 (0.9%)
White and Black African	–	3 (0.9%)
Caribbean	–	2 (0.6%)
Gypsy or Irish Traveler	–	1 (0.3%)
Pakistani	–	1 (0.3%)
Bangladeshi	–	1 (0.3%)
Chinese	–	1 (0.3%)
African	–	1 (0.3%)
Employment status[a]		
Employed, full-time work	91 (30.2%)	90 (28.2%)
Employed, part-time work	23 (7.6%)	37 (11.6%)
Homemaker	17 (5.6%)	12 (3.8%)
Student	1 (0.3%)	–
Unemployed	8 (2.7%)	21 (6.6%)
Retired	140 (46.5%)	145 (45.5%)
Disabled	29 (9.6%)	17 (5.3%)

Notes: Percentages are based on the total for the respective column. [a]Not mutually exclusive.
Abbreviations: SD, standard deviation; UK, United Kingdom; US, United States.

the US and 58.9 years in the UK (Table 2). Most participants reported their racial background to be white (US: n=270 [89.7%], UK: n=296 [92.8%]), and almost half reported being retired (US: n=140 [46.5%]; UK: n=145 [45.5%]).

The clinical characteristics of the participants are presented in Table 3. The mean self-reported BMI for participants was 30.9 among US participants and 29.5 among UK participants. There was a range in time since T2D diagnosis, with approximately one-third of the US sample reporting diagnosis within the past 5 years (33.9%), 5 to 10 years ago (32.9%),

Table 3 Sample Self-Reported Clinical Characteristics

Characteristic	US (N=301; 48.5%)	UK (N=319; 51.5%)
BMI[a] (kg/m^2), mean (SD) [min–max]	30.9 (6.8) [15–56]	29.5 (7.0) [18–62]
Current HbA1c level		
<5 (<30 mmol/mol)	0 (0.0%)	16 (5.0%)
5.00–6.99 (31–52 mmol/mol)	151 (50.2%)	69 (21.6%)
7.00–9.99 (53–85 mmol/mol)	87 (28.9%)	120 (37.6%)
≥10.00 (≥86 mmol/mol)	39 (13.0%)	33 (10.3%)
Do not know	24 (8.0%)	81 (25.4%)
Time since diagnosis		
≤5 years ago	102 (33.9%)	134 (42.0%)
6–10 years ago	99 (32.9%)	82 (25.7%)
≥11 years ago	100 (33.2%)	103 (32.3%)
Who currently treats your diabetes		
PCP/GP	277 (92.0%)	153 (48.0%)
Endocrinologist	21 (7.0%)	7 (2.2%)
Nurse	3 (1.0%)	99 (31.0%)
Other	0 (0.0%)	60 (18.8%)
Current health comorbidities[b]		
Angina	1 (0.3%)	2 (0.6%)
Anxiety	55 (18.3%)	41 (12.9%)
Arthritis	99 (32.9%)	49 (15.4%)
Chronic obstructive pulmonary disease/emphysema	13 (4.3%)	12 (3.8%)
Depression	60 (19.9%)	50 (15.7%)
Diabetes-related eye disease (retinopathy)	21 (7.0%)	35 (11.0%)
Diabetes-related kidney disease (renal disease)	10 (3.3%)	33 (10.3%)
Diabetes-related nerve damage (neuropathy)	50 (16.6%)	37 (11.6%)
Hypertension (high blood pressure)	188 (62.5%)	96 (30.1%)
Sleep apnea	50 (16.6%)	13 (4.1%)
Substance abuse	2 (0.7%)	0 (0.0%)
None of the above	32 (10.6%)	129 (40.4%)
Diabetes complications[b]		
Kidney complications	17 (5.6%)	26 (8.2%)
Eye complications	27 (9.0%)	41 (12.9%)
Foot complications (eg, non-healing wounds, diabetic foot ulcer, or amputation)	14 (4.7%)	41 (12.9%)

(*Continued*)

Table 3 (Continued).

Characteristic	US (N=301; 48.5%)	UK (N=319; 51.5%)
Nerve complications (eg, numbness or pain in the feet or hands)	68 (22.6%)	51 (16.0%)
None	206 (68.4%)	217 (68.0%)
Overall health		
Excellent	34 (11.3%)	23 (7.2%)
Very good	73 (24.3%)	48 (15.0%)
Good	117 (38.9%)	123 (38.6%)
Fair	68 (22.6%)	95 (29.8%)
Poor	9 (3.0%)	30 (9.4%)

Notes: [a]The standard calculation formula: [weight in kilograms / (height in meters x height in meters)] was used to calculate BMI. [b]Not mutually exclusive. Percentages are based on the total for the respective column.
Abbreviations: BMI, body mass index; HbA1c, glycated hemoglobin A1c; Max, maximum; Min, minimum; SD, standard deviation; UK, United Kingdom; US, United States.

and ≥11 years ago (33.2%). Slightly more UK participants (42.0%) were diagnosed within the past 5 years, with 25.7% and 32.3% being diagnosed 5 to 10 and ≥11 years ago, respectively. The majority of US participants (n=151, 50.2%) had an HbA1c of 5.00% to 6.99% (31–52 mmol/mol), whereas among UK participants, 37.6% (n=120) had an HbA1c of 7.00–9.99 and 25.4% (n=81) did not know their HbA1c. Participants reported a range of comorbid conditions, most commonly hypertension (45.8%).

DCE Internal Validity

Internal validity tests were used to evaluate the DCE data quality. Most participants passed both the dominance test (US: n=248 [82.4%]; UK: n=269 [84.3%]) and the stability test (US: n=257 [85.4%]; UK: n=258 [80.9%]). Almost all participants had response patterns indicating that they were appropriately attending to the choice tasks, as they did not always choose Option 1 or Option 2 (US: n=289 [96.0%]; UK: n=300 [94.0%]). Because these results are in line with other health DCEs in the literature[30] and there is evidence that suggests that excluding participants based on the results of internal validity tests can induce selection bias and reduce statistical efficiency,[31] all participants who completed the survey were included in the final analyses.

Participant Preferences

The RAI scores derived from participants' choices in the DCE are presented in Figure 2. RAI indicates how much changes in a particular attribute impacted participants' decisions relative to changes in the other attributes. Among US participants, HbA1c reduction was the most important driver of preferences (26.3%; 95% confidence interval [CI]: 20.5–32.1%), followed by delivery system (20.9%; 95% CI: 13.5–28.3%). Among UK participants, hypoglycemia was the most important attribute (32.8%; 95% CI: 25.7–40.0%) and HbA1c reduction the second most important (21.6%; 95% CI: 15.3–27.9%), with these two attributes making up over half of the RAI for UK participants.

The marginal utilities for each attribute level are plotted for the US and UK samples in Figure 3. For both samples, when choosing a T2D treatment, participants on average preferred greater HbA1c improvements; the single-use, pre-filled pen over the multi-use, dial-a-dose pen; lower risk of hypoglycemia; greater weight reductions; and lower frequency of nausea.
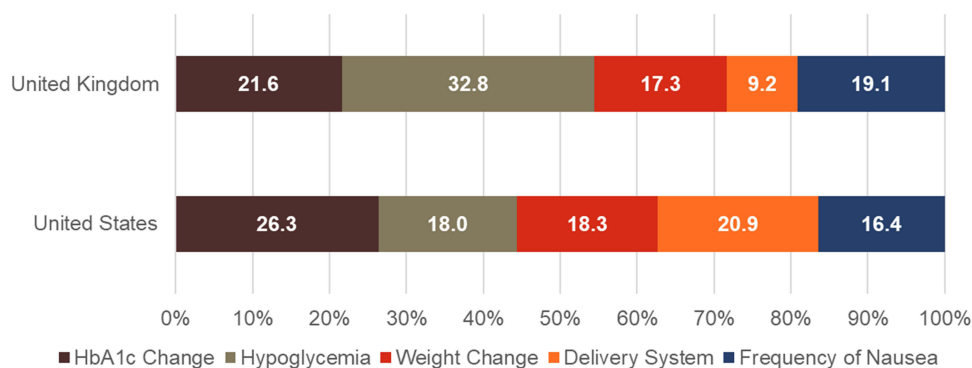
Figure 2 Relative attribute importance by country.
Abbreviation: HbA1c, glycated hemoglobin A1C.

Predicted Preferences for Tirzepatide vs Semaglutide 1mg Profiles

Predicted choice probability was also estimated for each dose of tirzepatide and semaglutide 1mg using the results of the DCE analyses (Figure 4). Assuming the availability of only tirzepatide or semaglutide 1mg, the predicted preference of tirzepatide in the US was 95.6% for the three doses combined (vs 4.4% for semaglutide 1mg) and in the UK was 86.3% for the three doses combined (vs 13.7% for semaglutide 1mg). Additionally, in each of the three non-experimental choice tasks in which participants were asked to choose between a treatment profile representing each of the tirzepatide doses (5mg, 10mg, and 15mg) vs a treatment profile representing semaglutide 1mg, more participants in the US preferred each dose of tirzepatide over semaglutide and more participants in the UK preferred tirzepatide 5mg and 10mg over semaglutide (all p<0.001) (Supplementary Figure S1).

Discussion

The treatment landscape for T2D continues to evolve, with newer medications presenting different options to patients and their physicians. The magnitude of decreases in HbA1c and weight loss associated with the novel GIP/GLP-1 RA medication have not been seen with prior diabetes treatments. Therefore, it is important to understand how these larger effects are valued by patients in the context of their medication decisions and relative to other important treatment attributes. Prior qualitative research has demonstrated that many of the trial participants who have taken the new GIP/GLP-1 RA medication have noticed improved glycemic control, weight loss, decreased appetite, and/or increased energy and that these changes were meaningful to them.[32] However, we do not know the relative importance of the changes in the various outcomes.

Based on the results of the current study, we conclude that overall, participants from both the US and UK preferred greater reductions in HbA1c, lower rates of hypoglycemia, greater weight loss, the single-use, pre-filled pen, and lower rates of nausea. This study demonstrated that the treatment preferences of individuals with T2D are greatly influenced by the ability of the treatment to reduce HbA1c. Among US participants, reduction in HbA1c was the single most impactful attribute on preferences, and among UK participants, it was the second most impactful after hypoglycemia. This result is not surprising given past research has demonstrated people with T2D in the US and UK place a great deal of importance on reaching near normoglycemia and associate this with a range of positive impacts.[18,19] Weight reduction also influenced preferences; however, this attribute was secondary to HbA1c reduction in both countries (US RAI: 18.3%; UK RAI: 17.3%). The RAI for delivery system was higher in the US (RAI: 20.9%) than in the UK (RAI: 9.2%), with patients in both countries preferring the single-use, pre-filled pen over the multi-use, dial-a-dose pen.

There were differences with respect to how changes in attributes influenced preferences of people with T2D in the US compared to the UK. First, improvements in HbA1c had a greater impact on preferences in the US. People with T2D in the UK tend to be less aware of their current HbA1c levels, for example, 8.0% of the US sample compared to 25.4% of the UK sample participating in the current study did not know their current HbA1c, and thus improvements in this attribute may be less salient to people in the UK. Second, hypoglycemia had a greater impact on preferences in the UK.

UK (N=319)
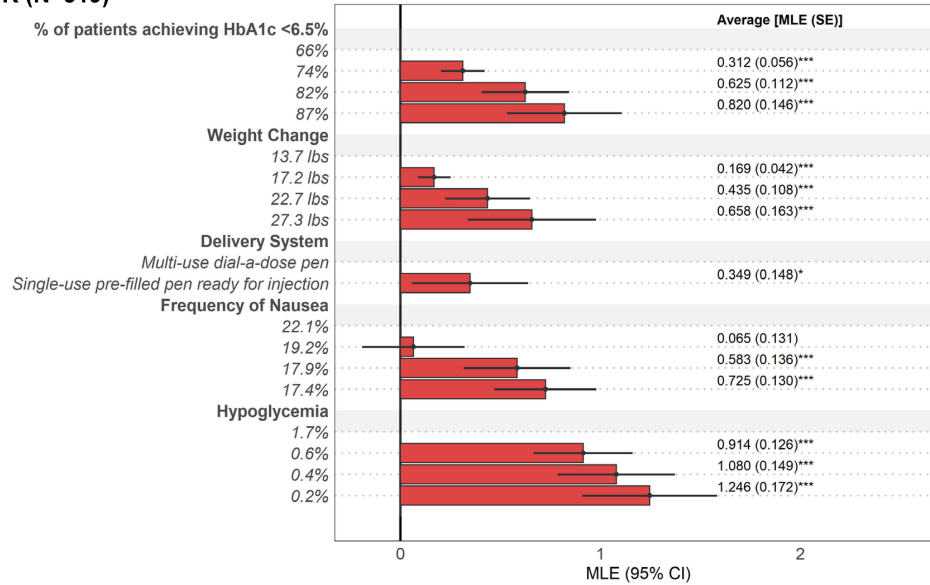
US (N=301)
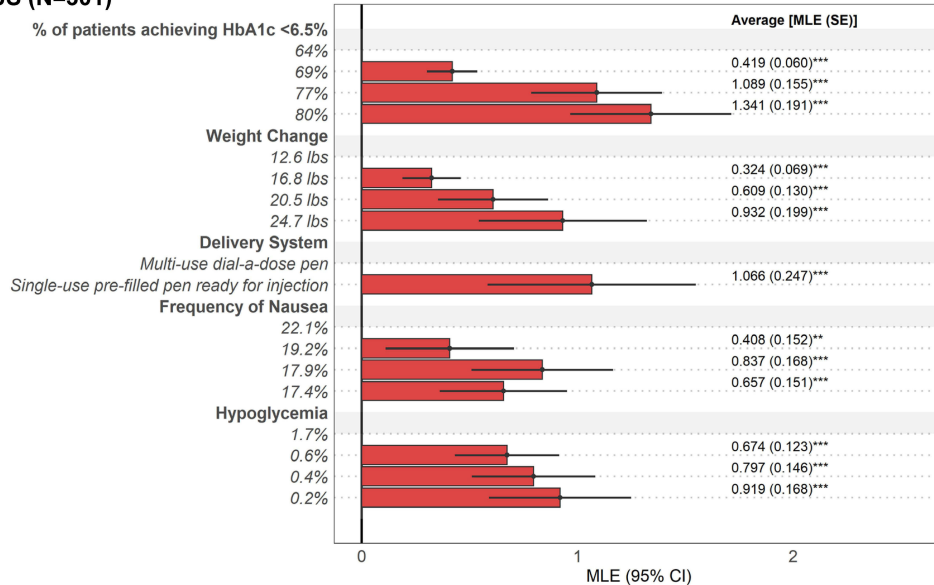
Figure 3 Marginal utilities by country. *p < 0.05; **p < 0.01; ***p < 0.001.
Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin A1C; MLE, maximum likelihood estimation.

This finding may reflect the fact that people with T2D in the UK are subject to certain restrictions, for example from driving, if they have a history of hypoglycemic events in the past year.[33] Further research should investigate the extent to which concerns related to maintaining a license to operate a vehicle might be related to preferences for avoiding medications associated with greater risk of hypoglycemia.

Perhaps not surprisingly, the results of the current study differ from those of prior studies.[24,25] In several prior studies, frequency of administration (daily vs weekly) was included as an attribute, as this was a relevant differentiator for the medications of interest. This particular attribute was often of high importance to participants. However, frequency of administration was not a factor in this study given both products are dosed weekly. In addition, the attributes of greatest importance in the current study (eg, HbA1c reduction, hypoglycemia and weight reduction) were of much less importance in the prior studies. This is likely because the magnitude of the improvements in each of these attributes

UK (N=319)

US (N=301)
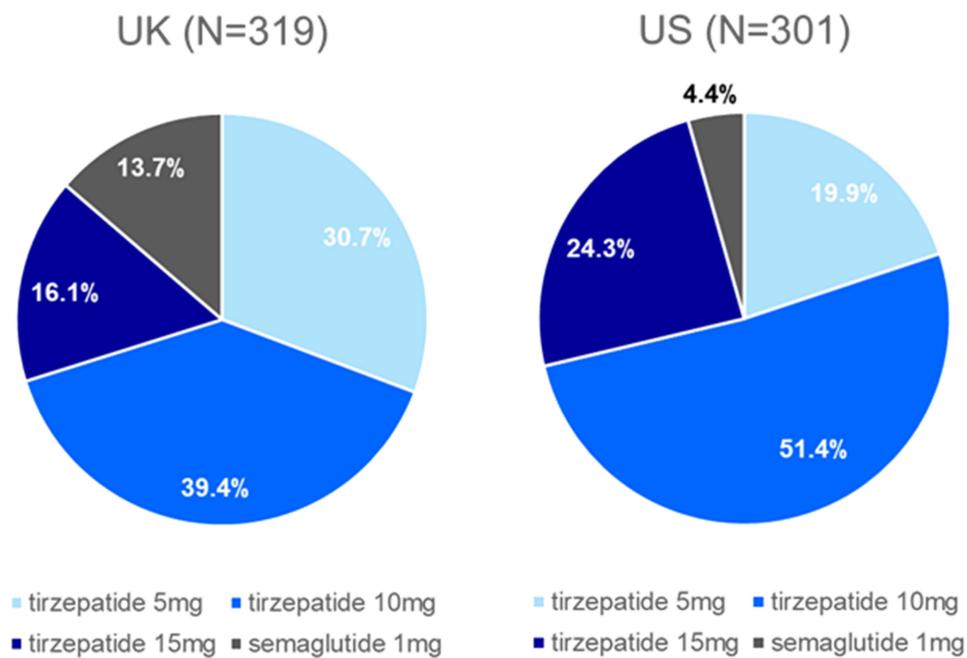
Figure 4 Predicted preference for tirzepatide and semaglutide.
Abbreviations: UK, United Kingdom; US, United States.

was much larger in this study than in those prior, reflecting the current treatment landscape. Thus, when considering much larger and more salient changes from the patient perspective, this resulted in significantly stronger preferences for improvements in these attributes.

Prior research has demonstrated that improvements in HbA1c, and specifically reaching near normoglycemia, is both meaningful and important to people with T2D in the US and UK.[18,19] This study demonstrates that the properties of tirzepatide, a novel, weekly, GIP/GLP-1 RA for T2D are valuable to people with T2D living in the US and UK. The tirzepatide efficacy and safety profiles differ from those of other T2D treatments that are currently available. Most notably, tirzepatide results in substantial reductions in HbA1c and significantly greater weight reduction than other treatments. This study demonstrated the importance of these benefits from the patient perspective, particularly when the magnitude of the improvements is large.

This information may be useful for clinicians when discussing available treatment options with their patients with T2D. This could lead to greater treatment satisfaction, and ultimately better adherence, although further research is needed to determine whether treatments that better match patients' preferences result in better adherence.

There are some limitations which should be considered when interpreting the results of this study. First, all data were self-reported, including participants' clinical data. Second, participants in this study were people with T2D taking oral medications and who were naïve to injectable medications. While the sample was fairly diverse, it was not necessarily fully representative of the US or UK T2D populations. The preferences of the participants in this study may not be generalizable to all people with T2D. Third, the SURPASS-2 trial did not assess long-term complications associated with T2D, and therefore these attributes, such as outcomes related to cardiovascular or kidney disease, were not included in this study.

Conclusion

While several studies have previously examined the treatment preferences of people with T2D, this study added to the existing literature by highlighting how the greater magnitude of HbA1c decrease and weight loss associated with the new class of GIP/GLP-1 RA medication impacts the preferences of people with T2D. This study demonstrated that HbA1c reduction, weight

reduction and frequency of hypoglycemia are key drivers of the preferences of people with T2D. Overall, people with T2D are likely to prefer medication profiles associated with tirzepatide, a novel GIP/GLP-1 RA over semaglutide 1mg, a GLP-1 RA.

Abbreviations

AE, adverse event; BMI, body mass index; CI, confidence interval; DCE, discrete choice experiment; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; HbA1c, glycated hemoglobin A1c; IFU, Instructions for Use; MXL, mixed logit model; RA, receptor agonist; RAI, relative attribute importance; SD, standard deviation; SGLT2, sodium–glucose cotransporter 2; T2D, type 2 diabetes.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval

This study received approval from Ethical & Independent Review Services [Study Number: 21181-01] on October 29, 2021. E&I is a central independent review board (IRB) that was used because there are not internal IRBs at the authors' institutions. The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments.

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Disclosure

Heather L Gelhorn is an employee of Evidera, a consultancy that provides scientific consulting services to pharmaceutical companies. Melissa M Ross is an employee of Evidera, a consultancy that provides scientific consulting services to pharmaceutical companies. Andrea Schulz is an employee of Evidera, a consultancy that provides scientific consulting services to pharmaceutical companies. Gabriela Fernandez is an employee of Evidera, a consultancy that provides scientific consulting services to pharmaceutical companies. Beatrice Osumili is an employee and shareholder of Eli Lilly and Company. Katelyn Brown is an employee and shareholder of Eli Lilly and Company. Kristina S Boye is an employee and shareholder of Eli Lilly and Company. The authors report no other conflicts of interest in this work.

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