

Patients' with type 2 diabetes willingness to pay for insulin therapy and clinical outcomes

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ABSTRACT

Objectives: This study assessed patient preferences, using willingness to pay as a method to measure different treatment characteristics or attributes associated with injectable insulin therapy in patients with type 2 diabetes.

Research design and methods: Adults with type 2 diabetes in 12 countries, diagnosed >6 months prior and receiving insulin for >3 months, were recruited through a representative online panel. Data were collected via online questionnaire and analyzed using a standard choice model for discrete choice experiment.

Results: A total of 3758 patients from North America (n=646), South America (n=1537), and Europe (n=1575) completed the study. Mean glycated hemoglobin (HbA_{1c}) levels in North America, South America, and Europe were 63 mmol/mol (7.9%), 75 mmol/mol (9.0%), and 64 mmol/mol (8.0%), respectively. In the three regions, monthly willingness to pay was US\$116, US\$74, and US\$92, respectively, for a 1%-point decrease in HbA_{1c}; US\$99, US\$80, and US\$104 for one less major hypoglycemic event per year; and US\$64, US\$37 and US\$60 for a 3 kg weight decrease. To avoid preinjection preparation of insulin, the respective values were US\$47, US\$18, and US\$37, and US\$25, US\$25, and US\$24 for one less injection per day. Among respondents on basal-only insulin who had previously tried a more intensive regimen, reasons for switching back included difficulty in handling multiple injections and risk of hypoglycemic events.

Conclusions: Reducing HbA_{1c}, frequency of major hypoglycemic events and weight decrease were the highest valued outcomes in each region. The administrative burden of injections was also considered important.

INTRODUCTION

The economic and clinical burden of diabetes is large, both for healthcare systems, and the individuals and their families living with diabetes.¹ In 2013, 382 million people worldwide were estimated to have diabetes, of which 90% had type 2 diabetes.^{1 2} Globally, healthcare costs to manage diabetes and its complications totaled US\$548 billion

Key messages

- Assessing willingness to pay can be used to understand patient preference for different treatment characteristics or attributes of injectable insulin therapy for type 2 diabetes.
- Reducing glycated hemoglobin, fewer major hypoglycemic events and weight decrease were the characteristics/attributes of injectable insulin therapy valued highest by respondents.
- Respondents on basal-only insulin who had previously tried a more intensive regimen cited difficulty in handling multiple injections, risk of weight gain, and risk of hypoglycemic events as the reasons for reverting to basal-only.

in 2013, equivalent to 11% of total worldwide health expenditure.¹

Recommended glycaemic goals are achieved by less than 50% of people with type 2 diabetes.³⁻⁶ Contributing to this are negative patient beliefs about the efficacy and safety of medication, and increasing complexity of therapies that may produce barriers to insulin treatments and may have an impact on medication adherence.^{4 7 8} Poor glycaemic control has a longer term impact on clinical outcomes and associated costs, as well as short-term effects on patient symptoms and quality of life.⁹ As such, it is important to understand how people with type 2 diabetes perceive the management of their condition and what they will accept in terms of impact on their daily lives. This may assist treatment strategies and support patient adherence.

Patient preferences for treatments have been shown to influence adherence to treatment in type 2 diabetes, affecting glucose lowering efficacy and overall burden of disease.^{3 10-12} For instance, it is likely that some people with diabetes already make preference decisions on aspects, or attributes, of their treatment, for example, accepting poorer glycaemic control and a higher risk of long-term complications in return for fewer episodes of hypoglycemia.¹³

One method of assessing patient preference for different treatment characteristics (attributes) is by measuring willingness to pay (WTP). WTP is defined as the amount of money an individual is willing to give up in order to procure goods or a service.^{14 15} It can be derived from discrete choice experiments^{3 16} based on two key premises that (1) treatments can be described by their characteristics (attributes), and (2) the extent to which an individual values the treatment depends on the nature and levels of these characteristics. This is particularly relevant for people who require treatment intensification as the disease progresses, in order to maintain glycaemic control. Measurement of WTP in diabetes has been demonstrated previously via discrete choice experiments in several studies.^{3 11 17} This approach allows the relative importance of treatment attributes and the respondents' WTP to obtain or avoid attributes to be determined.¹⁸ This provides insight into which characteristics of a treatment regimen would most likely be preferred by people with type 2 diabetes.¹⁸

Data from large studies investigating WTP in type 2 diabetes are limited. The current study, using methodology similar to that used by Bogelund *et al.*³ was conducted in 12 countries across North and South America and Europe, making it the largest WTP study to date.

The study aimed to investigate patient preferences for different clinical outcomes and administration burden of insulin treatments, and to assess a measurement of respondents' WTP for several aspects of treatment or attributes related to injectable insulin therapy, with assessment of the relative importance of each attribute.

METHODS

Patients

Patients were recruited from a web-based panel derived from members recruited via telephone or online advertisements. Patients consented to participate and involvement in the study was voluntary. Respondents were required to have been diagnosed with type 2 diabetes >6 months and be receiving subcutaneous injection of insulin for >3 months but not via pump therapy. Data were collected between August 2014 and February 2015 from respondents in North America (USA and Canada), South America (Chile, Colombia, Brazil, Argentina, and Mexico) and Europe (UK, France, Italy, Germany, and the Netherlands).

Design

The study was a cross-section study design. Six focus groups were conducted to gain insights into the daily life of people with type 2 diabetes, and to identify and validate the relevant diabetes treatment attributes for inclusion in the survey. The focus groups were held in Manchester, UK (n=4; n=6), Paris, France (n=6; n=7 plus 2 individual interviews), and Philadelphia, USA (n=7; n=8). Participants were asked to discuss the aspects of

diabetes treatment relevant to them, and to rank these aspects according to importance in their daily life. Participants also gave recommendations on how to describe each aspect to ensure relevance for people with diabetes. Finally, they were asked to assign values to specific improvements in each aspect. These findings were consolidated across the three regions and the most important features for patients with diabetes were selected as the attributes for inclusion in the online study questionnaire.

The questionnaire took approximately 15 min to complete and comprised six sections: (1) patient demographics; (2) attitudes of people with type 2 diabetes towards diabetes; (3) current and target HbA_{1c}; (4) hypoglycaemic events; (5) previous and current treatment and perceptions; and (6) WTP. This section was constructed around the core aspects of treatment or attributes, with a set of associated levels assigned to each attribute based on insights from the focus groups (table 1). Hypoglycaemic events were defined as either 'major', if requiring assistance from another person to effect recovery; or 'minor', estimated to account for 88–98% of all events,^{19–21} and defined by the ability to self-treat.^{22 23}

The descriptive levels for each attribute were determined based on insights from the focus groups. The degree of reduction in HbA_{1c} and weight was assigned according to standard clinical practice.

The descriptive levels for minor and major hypoglycaemic events were based on insights from the focus groups and a previous study by Evans *et al.*²⁴ The descriptive levels for the other attributes (number of injections and preparation of insulin by rolling and inverting pen or vial) were determined by treatment guidelines for use of insulin. The levels for the payment attributes were based on the focus groups and results from Jendle *et al.*¹⁶

From all possible combinations of attribute levels, a series of choice sets was derived using balanced, orthogonal, fractional, factorial design, generated using the Ngene discrete choice experimental design software system (developed by Choice Metric Pty Ltd)—see table 1 for an example.

This approach ensured parameter estimates were uncorrelated and could be determined independently of other attributes, and attribute levels occurred with equal frequency within the profiles, thus supporting robust results for all levels.

Each choice set presented attributes and levels for two different hypothetical diabetes treatments with payment levels documented as direct 'out of pocket' costs per month. Respondents were asked to select the preferred treatment option within each scenario, providing a hypothetical trade-off, which formed the basis of the analysis. In order to maximize the information gathered from the respondents, each respondent was randomly assigned to one of four blocks of these questions, each block consisting of nine choice sets.

Table 1a Clinical and convenience attributes related to insulin treatment; **Table 1b** Typical scenario choice sets for WTP

1a Core attributes	Levels for each attribute	
Change in HbA _{1c}	▶ 1%-point reduction in HbA _{1c}	
	▶ No change	
Number of minor hypoglycemic events	▶ 52 per year	
	▶ 12 per year	
	▶ 4 per year	
	▶ 0 per year	
Number of major hypoglycemic events (per 12 months)	▶ 1 per year	
	▶ 0 per year	
Preparation of insulin (rolling and inverting the pen or vial)	▶ Preparation of insulin	
	▶ No preparation of insulin	
Number of injections per day	▶ 1 injection per day	
	▶ 2 injections per day	
	▶ 4 injections per day	
Change in weight	▶ Weight increase of 1 kg	
	▶ Remain the same weight	
	▶ Weight decrease of 3 kg	
	▶ Weight decrease of 5 kg	
Payment per month (out-of-pocket expense)	▶ US\$27.75	
	▶ US\$61.05	
	▶ US\$127.65	
	▶ US\$277.50	

1b Typical WTP scenario choice sets	Treatment A	Treatment B
HbA _{1c} levels	No change	Reduction of 1%
Number of minor hypos	0 yearly	52 yearly
Number of major hypos	1 yearly	0 yearly
Weight change	No change	Lose 3 kg
Preparation of insulin before injection (rolling and inverting the pen or vial)	No	Yes
Number of insulin injections	1 daily injection	4 daily injections
Payment per month (out-of-pocket)	US\$277.50	US\$61.05
Which treatment do you prefer?		

HbA_{1c}, glycated hemoglobin; WTP, willingness to pay.

The inclusion of a test question presenting a scenario with one profile better than the others for all attributes—that is, no trade-off required—ensured respondents understood the overall concept of ‘trade-off’. Respondents are likely to have different preferences for certain attributes. Therefore, in the choice set used for the test question, only the number of minor and major hypoglycemic events, and the level of payment, were different in the two treatment profiles. As per published practice,²⁵ any respondents not selecting the superior profile were excluded. In this instance, respondents choosing the treatment with both a higher number of hypoglycemic events and a higher payment were excluded.

The questionnaire was developed in English, and translated using forward and backwards translation to the native languages of the countries included in the survey. The study was performed according to the Declaration of Helsinki w/c 14 December 2014, and anonymity of respondents was preserved in accordance with European Society for Opinion and Marketing Research, and European Pharmaceutical Market

Research Association regulations.^{26 27} Ethical approval was obtained from Institutional Review Board Services, Canada. Monetary values recorded in other currencies were converted to US\$ for reporting, using the exchange rates prevalent in December 2014.²⁸

Analysis

Data were validated and checked for consistency and error before conducting the statistical analyses with the SAS analytical software package (V.9.4, SAS Institute Inc, North Carolina, USA). WTP for the different attributes was determined using a standard mixed multinomial logit model approach. The probability of choosing one option ‘j’ from n_i in a choice scenario (where there are n_i=2 possible options in each scenario choice set C_i) is defined by the equation^{3 29}

$$P(j) = \frac{\exp(\chi'_{ij}\beta)}{\sum_{k \in C_i} \exp(\chi'_{ik}\beta)}$$

The estimated parameters β, will express preference weights for each attribute level. The WTP values for the

attribute levels were calculated by dividing the estimated coefficients, β , for each attribute, by the coefficient of payment. The rationale underlying this approach was derived from the economic theory of demand, in which these calculated ratios are known as marginal rates of substitution.³⁰

The linearity of the relevant attributes was then tested using a standard likelihood ratio test. This was the case for weight loss, minor hypoglycemia events and number of daily insulin injections. All these attributes exhibited linearity and so the linear function was introduced into the basic model. Interaction effects were tested according to a predefined statistical analysis plan. The results for the linear variables were then subsequently calculated per unit, for example, WTP for a weight loss of 1 kg or 2 kg. Owing to the sample size required for robust analysis, WTP data were assessed by region only. The costs used in the discrete choice experimental design were presented using the currency of each country. When converting the currencies, the levels of payment were corrected for purchasing power in each country.

Since WTP data are calculated as the ratio between two stochastic variables, CIs cannot be derived directly from the parameter estimates of the conditional logit estimations. Therefore, an adapted bootstrapping methodology was applied—a method originally developed to derive the estimate of SE of an arbitrary estimator.³¹ The bootstrap methodology simulates the results from a random sample of the actual data available.³² Empirical research suggests that the best results are obtained when the repeated samples are the same size as the original sample and therefore the repetition is performed with replacement.³² For deriving the CIs for current WTP results, 10 000 iterations were carried out.³²

The WTP design and analysis were performed in accordance with the International Society for Pharmacoeconomics and Outcomes Research Good Practice for Conjoint Analysis in Health.^{33 34}

RESULTS

Participants

Results from 3758 respondents with type 2 diabetes were available for analysis, representing North America (USA and Canada; n=646), South America (Brazil, Chile, Colombia, Argentina, and Mexico; n=1537), and Europe (UK, Germany, the Netherlands, Italy, and France; n=1575).

Participants' mean age in the three regions ranged between 48.1 and 54.5 years, with the majority of respondents being male in all three regions. The mean values for duration with diabetes, duration on insulin, and BMI, are presented by region in [table 2](#) along with socio-demographic characteristics across the three regions.

In all three regions, basal-only insulin was the most frequently used insulin regimen, followed by basal-bolus insulin. Few respondents were on bolus-only and premix-

only treatment schemes. Full details of the type of insulin used are reported in [table 2](#).

Payment for insulin

In North America, the majority of respondents paid for at least some of their medication costs; in contrast, most respondents in Europe indicated that they made no payment. In South America, approximately half paid for their medication. Full details about payment for medication are reported in [table 2](#).

HbA_{1c} levels

Approximately two-thirds of respondents in each region were aware of their HbA_{1c} levels, with a slightly lower percentage being aware of their target HbA_{1c}. The mean reported HbA_{1c} levels in North America, South America, and Europe, were 63 mmol/mol (7.9%), 75 mmol/mol (9.0%) and 64 mmol/mol (8.0%), respectively.

Hypoglycemic events

Full details pertaining to HbA_{1c} levels and hypoglycemic events are presented by region in [table 2](#).

Barriers to treatment intensification

A proportion of respondents had reverted back to basal-only insulin from an intensified regimen. In North America, most had switched back from basal-bolus insulin (52.6% (41/78)), followed by 38.5% (30/78) from premixed insulin, and 9.0% (7/78) from basal insulin plus a glucagon-like peptide receptor antagonist (GLP-1 RA; [table 3](#)). In South America this was 57.8% (115/199), 32.7% (65/199), and 9.5% (19/199), respectively, with 48.8% (79/162), 37.7% (61/162), and 13.6% (22/162) in Europe.

Difficulty in handling multiple injections as well as risk of weight gain and hypoglycemia were the most frequently cited reasons for reverting back to basal-only therapy. An analysis of patients with type 2 diabetes who had reverted to basal-only insulin after previously switching to basal-bolus, premix insulin or a GLP-1 RA in combination with basal insulin, is shown in [table 3](#).

Analysis of willingness to pay

Results of the WTP analysis are presented in [figure 1](#) as monetary values per month. All treatment attributes were significant predictors of choice ($p < 0.05$), with high monetary values placed on efficacy and safety outcomes. In North America, respondents were willing to pay US\$116 for a 1%-point decrease in HbA_{1c} (95% CI (79 to 158)). In South America, this was US\$74 (CI (54 to 97)), with US\$92 (CI (69 to 117)) in Europe. WTP for 'one less major hypoglycemic event per year' was US\$99 (95% CI (67 to 136)), US\$80 (CI (62 to 102)), and US\$104 (CI (84 to 128)), and for 'one less minor hypoglycemic event per month', WTP was US\$34 (CI (25 to 43)), US\$21 (CI (16 to 26)), and US\$22 (CI (17 to 28)) in North America, South America, and Europe, respectively. WTP

Table 2a Baseline characteristics of study respondents; **Table 2b** Glycemic control and hypoglycemia

Category	All regions n (%)	North America n (%)	South America n (%)	Europe n (%)
Table 2a				
<i>Clinical</i>				
Male/female	58.0%	57.7	54.1%	61.9%
Mean age (years)	51.4	54.5	48.1	53.4
Mean duration with diabetes (years)	10.7	12.4	9.8	11.0
Mean duration with insulin (years)	5.7	6.4	4.8	6.3
Mean BMI(kg/m ²)	30.3	33.5	29.1	30.3
Live alone	21.1%	29.6%	12.9%	25.7%
Have children	74.8%	60.5%	83.8%	71.8%
Married or partnered	68.7%	62.7%	68.1%	71.6%
College/university degree	46.1%	44.1%	52.0%	41.2%
In paid employment or self-employed	37.6%	32.0%	40.1%	37.3%
Monthly household income before tax=<approximately ≤US\$3 000	31.5%*	32.8%	28.0%*	34.5%†
<i>Type of insulin used</i>				
Basal insulin only	1841 (49.0%)	274 (42.4%)	963 (62.7%)	604 (38.4%)
Bolus insulin only	490 (13.0%)	59 (9.1%)	166 (10.8%)	265 (16.8%)
Basal and bolus insulin	1020 (27.1%)	224 (34.7%)	274 (17.8%)	522 (33.1%)
Premixed only	332 (8.8%)	70 (10.8%)	106 (6.9%)	156 (9.9%)
Other combination	75 (2.0%)	19 (2.9%)	28 (1.8%)	28 (1.8%)
<i>Payment of medication</i>				
Yes, I pay for all of it	657 (17.5%)	123 (19.0%)	391 (25.4%)	143 (9.1%)
Yes, I pay for some of it	1011 (26.9%)	335 (51.9%)	382 (24.9%)	294 (18.7%)
No, I don't pay for any of it	2090 (55.6%)	188 (29.1%)	764 (49.7%)	1138 (72.3%)
Table 2b				
<i>HbA_{1c}</i>				
HbA _{1c} and patient awareness				
Number of respondents knowing their HbA _{1c}	2441 (65.0%)	395 (61.2%)	964 (62.7%)	1082 (68.7%)
Respondents' mean HbA _{1c}	67 mmol/mol (8.3%)	63 mmol/mol (7.9%)	75 mmol/mol (9.0%)	64 mmol/mol (8.0%)
Number of respondents who are aware of target HbA _{1c}	2308 (61.4%)	392 (60.7%)	909 (59.1%)	1007 (63.9%)
<i>Hypoglycemic events</i>				
Have respondents ever experienced a minor hypoglycemic event?				
Yes	2950 (78.5%)	500 (77.4%)	1202 (78.3%)	1248 (79.2%)
Frequency of minor hypoglycemic events				
3 times weekly	256 (8.7%)	31 (6.2%)	112 (9.3%)	113 (9.1%)
Once weekly	757 (25.7%)	109 (21.8%)	323 (26.9%)	325 (26.0%)
Once monthly	805 (27.3%)	147 (29.4%)	317 (26.4%)	341 (27.3%)
Once every 3 months	420 (14.2%)	87 (17.4%)	163 (13.6%)	170 (13.6%)
Less than once every 3 months	712 (24.1%)	126 (25.2%)	287 (23.9%)	299 (24.0%)
Never	710 (18.9%)	119 (18.4%)	294 (19.1%)	297 (18.9%)
Mean number of events yearly	25.0	20.8	26.2	25.5
Have respondents ever experienced a major hypoglycemic event?				
Yes	929 (24.7%)	178 (27.6%)	345 (22.5%)	406 (25.8%)
Number of major hypoglycemic events during the past 12 months				
0	2754 (73.3%)	446 (69.0%)	1148 (74.7%)	1160 (73.7%)
1–2	391 (10.4%)	69 (10.7%)	137 (8.9%)	185 (11.7%)
3–4	166 (4.4%)	44 (6.8%)	47 (3.1%)	75 (4.8%)
5–6	75 (2.0%)	13 (2.0%)	23 (1.5%)	39 (2.5%)
7–8	24 (0.6%)	8 (1.2%)	4 (0.3%)	12 (0.8%)
9–10	49 (1.3%)	9 (1.4%)	21 (1.4%)	19 (1.2%)
More than 10	108 (2.9%)	14 (2.2%)	60 (3.9%)	34 (2.2%)

*The number for South America is an estimate, since different country-specific currencies were used.

†The value for Europe is based on the % of respondents with a monthly household income of ≤€1999.

BMI, body mass index; HbA_{1c}, glycated hemoglobin level.

Table 3 Patients with type 2 diabetes currently using basal insulin, previously intensified with bolus or GLP-1 RA, or premixed insulin

Patients with type 2 diabetes	Region			
	All regions	North America	South America	Europe
Total number of respondents	439	78	199	162
<i>Previously added bolus to basal insulin</i>				
Number of patients	235 (53.5%)	41 (52.6%)	115 (57.8%)	79 (48.8%)
Reasons for going back to basal insulin only				
Difficult to handle multiple injections	26.4%	29.3%	27.8%	22.8%
Risk of weight gain	25.1%	39.0%	17.4%	29.1%
Risk of hypoglycemia events	23.8%	24.4%	20.9%	27.9%
Difficult to calculate bolus dose	22.1%	14.6%	25.2%	21.5%
Other reasons	21.3%	22.0%	22.6%	19.0%
<i>Previously added GLP-1 RA to basal insulin</i>				
Number of patients	48 (10.9%)	7 (9.0%)	19 (9.5%)	22 (13.6%)
Reasons for going back to basal insulin only				
Difficult to handle multiple injections	29.2%	42.9%	31.6%	22.7%
Risk of hypoglycemic events	31.3%	0.0%	52.6%	22.7%
Risk of gastrointestinal (GI) side effects	18.8%	0.0%	26.3%	18.2%
Other reasons	31.3%	57.1%	10.5%	40.9%
<i>Previously switched to premixed insulin</i>				
Number of patients	156 (35.5%)	30 (38.5%)	65 (32.7%)	61 (37.7%)
Reasons for going back to basal insulin only				
Difficult to handle multiple injections	49.4%	36.7%	61.5%	42.6%
Risk of weight gain	34.6%	26.7%	27.7%	45.9%
Risk of hypoglycemic events	17.3%	20.0%	23.1%	9.8%
Other reasons	11.5%	23.3%	4.6%	13.1%

GLP-1 RA, glucagon-like peptide receptor antagonist.

for a 1 kg weight decrease was US\$21 (CI (14 to 29)), US\$12 (CI (8 to 16)), and US\$20 (CI (15 to 25)) in North America, South America, and Europe, respectively. For a

2 kg weight decrease, WTP was US\$43 (CI (27 to 59)), US\$25 (CI (17 to 33)), and US\$40 (CI (31 to 50)), respectively, while for 3 kg decrease, WTP was US\$64 (CI

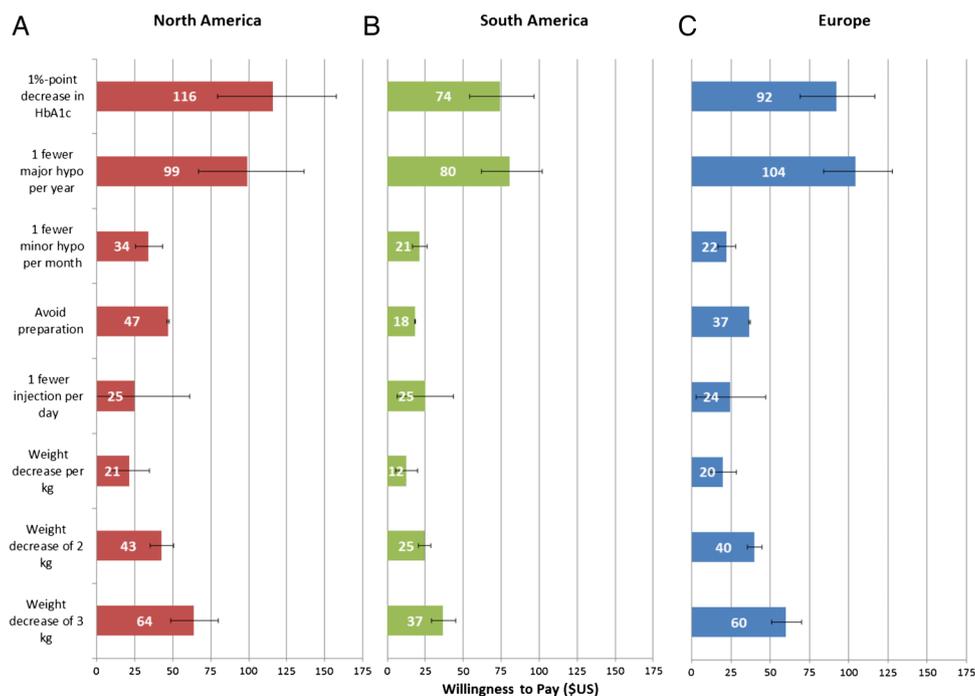


Figure 1 Willingness to pay (WTP) for clinical outcomes in separate regions: (A) (North America) (B) (South America) and (C) (Europe). HbA_{1c}, glycated hemoglobin.

(41 to 88)), US\$37 (CI (25 to 49)), and US\$60 (CI (46 to 75)). Additionally, in order to avoid preparation of insulin (eg, rolling and inverting the pen or vial), respondents were willing to pay US\$47 (CI (12 to 83)), US\$18 (CI (-0.27 to 37)), and US\$37 (CI (15 to 59)), respectively. For one less injection per day, WTP was US\$25 (CI (12 to 38)), US\$25 (CI (18 to 33)), and US\$24 (CI (16 to 33)), in North America, South America, and Europe, respectively.

An alternative way to present the outcomes of the analysis is by assessing the WTP of each attribute relative to one consistent attribute. In North America, comparing against 'reduction of minor hypoglycemic events per month by one', a 1%-point decrease in HbA_{1c} was valued 3.4 times higher (US\$116 vs US\$34); one less major hypoglycemic event per year 2.9 times higher (US\$99 vs US\$34); being able to avoid preparation of insulin 1.4 times higher (US\$47 vs US\$34), and a 3 kg decrease in weight 1.9 times higher (US\$64 vs US\$34). Also, WTP for one less minor hypoglycemic event per month was 1.4 times more than WTP for one less injection per day (US\$34 vs US\$25).

In South America, comparing against 'reduction of minor hypoglycemic events per month by one', a 1%-point decrease in HbA_{1c} was valued 3.5 times higher (US\$74 vs US\$21); one less major hypoglycemic event per year 3.8 times higher (US\$80 vs US\$21); a 3 kg decrease in weight 1.8 times higher (US\$37 vs US\$21), and one less injection per day 1.2 times higher (US\$25 vs US\$21). Additionally, one less minor hypoglycemic event per month was valued 1.2 times higher than being able to avoid preparation of insulin (US\$21 vs US\$18).

In Europe, comparing against 'reduction of minor hypoglycemic events per month by one', a 1%-point decrease in HbA_{1c} was valued 4.2 times higher (US\$92 vs US\$22); one less major hypoglycemic event per year 4.7 times higher (US\$104 vs US\$22); being able to avoid preparation of insulin 1.7 times higher (US\$37 vs US\$22); one less injection per day 1.1 times (US\$24 vs US\$22), and a 3 kg decrease in weight was valued 2.7 times higher (US\$60 vs US\$22).

DISCUSSION

To the best of our knowledge, this is the largest published international study reporting willingness to pay for different treatment attributes in type 2 diabetes care and outcomes related to subcutaneous injection of insulin. The results demonstrated the relative values people with type 2 diabetes place against different attributes of treatment. The principle findings showed that treatment attributes were significant predictors of choice ($p < 0.05$), with high monetary values placed on efficacy and safety outcomes. Respondents on basal-only insulin who had previously tried a more intensive regimen switched back citing the reasons as difficulty in handling multiple injections, risk of weight gain, and risk of hypoglycemic events.

Demographic split in the study population was in line with global data, with a slightly higher proportion of males. The reported frequency of hypoglycemic events is similar to previous findings of Bogelund *et al*³ in Denmark. Additionally, the estimated annual rate of major hypoglycemic events in people with type 2 diabetes was measured by the HAT study at 2.5 events per year, while in the current study, at least one major hypoglycemic event was experienced by 22% of respondents across all regions during the past 12 months.³⁵ Unlike previous studies, the current study presented data for both, major and minor hypoglycemic events, allowing demonstration of the relative value attributed to each. Based on the results, avoidance of major hypoglycemic events is most highly valued in Europe and South America relative to the other attributes. In North America, WTP valuation was highest for a 1%-point reduction in HbA_{1c}. Overall, nearly half of the respondents were taking basal-only insulin, accounting for the largest treatment population across all three regions. Of these, nearly a quarter of the respondents had reverted back to basal-only insulin following previous treatment intensification. Among the perceived barriers investigated, the number of daily injections, the risk of hypoglycemic events, and the risk of weight gain, were most frequently noted as reasons for discontinuing and reverting back to basal insulin. This supported the findings of the WTP analysis in that people with type 2 diabetes are keen to avoid the perceived negative outcomes of intensifying their insulin treatment. With regard to the number of daily injections, the WTP valuation for one less injection per day may appear relatively low. However, patients may potentially administer several injections on a daily basis, so considering only one less injection may not appear to be of great importance initially.

The current findings support those from country specific studies in Sweden¹⁶ and Denmark³ that include people with type 2 diabetes value improvements in treatment profile, and the resulting health and lifestyle benefits. The present results are also consistent with those from Lloyd *et al*,³⁶ where avoidance of hypoglycemia or weight gain, and the reduction in the number of daily injections, were associated with positive WTP values relative to other attributes. For instance, WTP in North America for one less major hypoglycemic event per year, to decrease weight by 1 kg, and to administer one less injection per day, is US\$99, US\$21 and US\$25 per month, respectively. In the US study by Hauber *et al*,¹⁷ the reduction in average glucose (HbA_{1c}) is valued most highly by respondents, which is reflected by findings in this study, where respondents from North America were most willing to pay for a 1%-point decrease in HbA_{1c} (US\$116 per month). This was also consistent with findings in Denmark,³ where the WTP was €99 per month for the same attribute (US\$126 per month, using December 2014 exchange rate²⁸). WTP varied across the different attributes. However, as WTP is the patients' best assessment of the value, these may differ from real

life situations and it is likely that the relativeness between WTP values will provide a better indication of the relative importance of each attribute. For instance, in North America, 'one less minor hypoglycemic event per month' was valued low in comparison to the value of a 3 kg decrease in weight (US\$34 per month vs US\$64 per month). However, despite a relatively low WTP, minor hypoglycemic events are associated with a reduction in quality of life,^{37 38} and can interrupt and affect the ability to carry out day-to-day tasks.³⁹ It may therefore be relevant to further analyze how patients value other clinical aspects compared to minor hypoglycemic events. In contrast, 'one less major hypoglycemic event per year' was valued high in comparison with other attributes, and valued at the same level as reducing HbA_{1c} by 1%-point. The difference between regions in terms of the attribute that was valued the most by respondents is another area of particular interest; respondents from North America valued a 1%-point reduction in HbA_{1c} the highest, compared to Europe, where a reduction in major hypoglycemic events was most valuable. Specific treatment scenarios demonstrating the applicability of the study findings (eg, the value of reducing the number of injections per day or not gaining weight) can be established. For a patient with type 2 diabetes who requires treatment intensification after failure of basal insulin in combination with oral agents, combination injectable therapy is recommended, consisting of either adding a GLP-1 RA or bolus insulin to the current therapy, or switching to premixed insulin.⁴⁰ Intensifying treatment by adding bolus insulin usually requires three additional injections a day at meal-times on top of the current basal insulin (minimum once daily), resulting in a regimen with a minimum of four injections daily. Alternatively, the patient could add a GLP-1 RA to the current basal insulin (minimum 2 daily injections) or switch to premixed insulin, which requires a total of two injections per day. According to this study, moving from a treatment with four injections per day to that with only two injections per day, was valued at US\$50 per month in North America and South America, and US\$48 per month in Europe, assuming that all other treatment aspects are the same. Another example that illustrates the applicability of the findings from this study refers to weight gain associated with insulin therapy. Although many diabetes treatments cause weight gain, some have shown to be weight neutral or even to result in weight loss. For a given treatment that provides a weight loss of 3 kg compared to a treatment with no weight change, all other things remaining equal, patients would value this at US\$64 per month in North America, US\$37 per month in South America, and US\$60 per month in Europe. These examples of the applicability of the value of individual treatment attributes could potentially be combined for a more in-depth assessment and exploration of the WTP for type 2 diabetes treatments that provide improvements in several of the attributes examined in this study.

There are a number of potential limitations of the study, associated with the methodology. As many patients may not regularly experience out-of-pocket expenditure for their healthcare requirements (eg, patients in Europe), the WTP estimates may differ from the value patients would pay for improvements in clinical outcomes in real-life situations. Hence the relative importance of each attribute might be a more relevant outcome of this study than the individual WTP estimates. Purchasing power is the preferred way of comparing monetary values across countries, but it is also introducing an additional uncertainty. Although the discrete choice experiments methodology is designed to restrict the potential for strategic answers from respondents, there is still potential for stated preferences within each scenario presented in the study to differ from those made by the same individual in a real-life situation. Recruitment was through online panels requiring respondents to have an email address and an adequate degree of computer literacy, which may have introduced selection bias. It is also acknowledged that, despite clear description in the questionnaire, some respondents may yet have interpreted the out-of-pocket expense as a one-off payment, rather than a monthly outlay. Furthermore, the questionnaire is self-reported, without validation of clinical characteristics by healthcare providers, resulting in potential for recall bias.

In conclusion, the present study has shown people with type 2 diabetes value improved clinical outcomes, and reduced burden of preparing and injecting insulin. Reducing HbA_{1c} and the number of major hypoglycemic events were attributes that generated some of the higher WTP values, but the burden associated with the preparation of dosing insulin was also considered important. Patient perceptions of the risks associated with intensifying insulin treatment may result in non-adherence and act as barriers to achieving treatment goals. Understanding patients' preferences can help to develop optimal treatment approaches for individuals with type 2 diabetes. This in turn could lead to improved clinical control through improved treatment adherence resulting in better clinical outcomes.

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