Original article

Avoidance of weight gain is important for oral type 2 diabetes treatments in Sweden and Germany: Patient preferences

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Abstract

Aims. – The aim of the study was to quantify patient preferences for outcomes associated with oral antidiabetic medications (OAMs) in Sweden and Germany through a discrete-choice experiment.

Methods. – Adults taking OAMs who had a self-reported physician’s diagnosis of type 2 diabetes mellitus (T2DM) made a series of nine choices between pairs of hypothetical profiles. Each profile had a predefined range of attributes: blood glucose control, frequency of mild-to-moderate hypoglycaemia, annual severe hypoglycaemic events, annual weight gain, pill burden and frequency of administration, and cost. Choice questions were based on an experimental design with known statistical properties. Bivariate probit analysis estimated the probabilities of choice of medication administration from patient characteristics and, conditional on that choice, preferences for treatment outcomes.

Results. – The final sample consisted of 188 Swedish and 195 German patients. For both countries, weight gain was the most important attribute, followed by blood glucose control. Avoiding a 5-kg weight gain was 1.5 times more important in Sweden and 2.3 times more important in Germany than achieving moderate blood glucose control, thereby, suggesting that blood glucose control is relatively more important to Swedish than to German patients. Least important outcomes were the number of daily pills (Sweden) and frequency of mild-to-moderate hypoglycaemia (Germany).

Conclusion. – Patients in both Sweden and Germany preferred OAMs not associated with weight gain.

Keywords: Oral antidiabetic medication; Discrete-choice experiment; Choice-format conjoint analysis; Patient preferences

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Résumé

Éviter la prise de poids est important pour le traitement par voie orale du diabète de type 2: la préférence des patients.

Objectif. – L’objectif de l’étude était de quantifier les préférences des patients vis-à-vis des résultats obtenus par les traitements antidiabétiques oraux en Suède et en Allemagne, via une analyse conjointe.

Méthodes. – Des sujets adultes recevant des traitements oraux antidiabétiques, rapportant par eux-mêmes un diabète de type 2 diagnostiqué par un médecin, ont répondu à une série de neuf choix entre différentes paires de profils hypothétiques. Chaque profil était pré-défini selon les attributs suivants: le contrôle glycémique, la fréquence des épisodes hypoglycémiques légers à modérés, le taux annuel d’hypoglycémies sévères, le gain de poids sur l’année, le nombre de comprimés et la fréquence d’administration, ainsi que le coût des traitements. Les choix proposés aux patients utilisaient un design expérimental avec des propriétés statistiques connues. Une analyse probit bivariée a estimé les probabilités de choix des patients sur leur modalité d’administration des traitements en fonction de leurs caractéristiques, et conditionné par ce choix, les préférences par rapport à chacun des résultats du traitement du diabète.

Résultats. – L’échantillon final était composé de 188 patients suédois et de 195 patients allemands. Dans ces deux pays, le gain de poids a été l’attribut le plus important, suivi par le contrôle glycémique. Éviter une prise de poids de 5 kg a été 1,5 fois plus important en Suède que d’obtenir un contrôle glycémique modéré et 2,3 fois plus important en Allemagne, c’est-à-dire que le contrôle glycémique a été relativement plus important

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for the patients suédois que pour les patients allemands. Le nombre de comprimés par jour a été moins important pour les patients suédois ainsi que la fréquence des épisodes hypoglycémiques légers à modérés pour les sujets allemands.

**Conclusion.** — Les patients en Suède et en Allemagne préfèrent les traitements antidiabétiques oraux qui ne produisent pas de prise de poids.

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**Mots clés :** Traitements antidiabétiques oraux ; Analyse conjointe ; Préférences des patients

1. **Introduction**

In Sweden, around 386,000 people (5.7% of the age-adjusted population) have a diagnosis of type 2 diabetes mellitus (T2DM) and about 141,000 people have undiagnosed T2DM [1]. In contrast, more than five million people in Germany (8% of the age-adjusted population) have a diagnosis of T2DM and an estimated 1.8 million people have undiagnosed T2DM [1]. Obesity is the most important risk factor for T2DM in Western societies [1–3].

Several international organizations have issued guidelines for the treatment of T2DM [4–7]. However, the recent position statement published by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) reiterates the importance of a patient-centered approach to diabetes management [6]. The authors recognize that it is ultimately patients who make the final decisions regarding their lifestyle, treatment and resource allocations, and that clinical guidelines “should be considered within the context of the needs, preferences, and tolerances of each patient”. Understanding what patients expect and value in managing chronic diseases, like diabetes, including both clinical outcomes and quality-of-life aspects of care, will play an increasingly important role in the future of diabetes treatment, and the patient’s perspective on these concepts is cited by the ADA and EASD as a significant area for future research [6].

Based on these recommendations, the primary objective of the present study was to quantify patient preferences for outcomes associated with oral antidiabetic medications (OAMs) in Sweden and Germany. The study followed best practices [8] in designing and administering a discrete-choice experiment (DCE), also known as a “choice-format conjoint analysis survey”, to identify patients’ preferences.

2. **Methods**

2.1. **The discrete-choice experiment**

The study used a DCE survey to elicit information on patient preferences for outcomes associated with OAMs. This systematic method is grounded in both psychology [9] and economics [10] for determining trade-offs to quantify the relative importance placed on various treatment outcomes [11,12]. The approach is based on the premise that treatments comprise a set of attributes or outcomes (such as, efficacy and side-effects) and that the relative importance or value of a particular treatment to an individual is a function of these attributes [13–16].

2.2. **The survey instrument**

Patient preferences for how to take their medication (once a day or twice a day) were elicited for six attributes of OAMs, including blood glucose control [improvement in glycated haemoglobin (HbA1c)], frequency of monthly mild-to-moderate hypoglycaemia, annual severe hypoglycaemic events, annual weight gain, number of pills taken daily and personal monthly cost. These attributes were chosen to describe OAMs after a review of package inserts and consultation with clinical experts. Each attribute had a range of levels (Table 1). These levels were designed to encompass the range observed in clinical practice as well as the range over which patients were willing to accept trade-offs among attributes.

Patients were shown a series of nine hypothetical OAMs, each featuring a different combination of levels for each attribute, and asked to indicate how they would take the medication (either once a day or twice a day). Taking the medication more frequently would result in comparatively better glucose control but would also be less convenient and more costly, and might result in a greater frequency of monthly hypoglycaemia. Fig. 1

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Levels in Germanya</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose control (HbA1c) for once a day treatment</td>
<td>Need some control (&gt; 7% but ≤ 8%)</td>
</tr>
<tr>
<td>Blood glucose control (HbA1c) for twice a day treatment</td>
<td>Need a lot more control (&gt; 8%)</td>
</tr>
<tr>
<td>Mild-to-moderate hypoglycaemias per month</td>
<td>Controlled (≤ 7%)</td>
</tr>
<tr>
<td>One severe hypoglycaemia (low) per year</td>
<td>Need some control (&gt; 7% but ≤ 8%)</td>
</tr>
<tr>
<td>Weight gain per year</td>
<td>None</td>
</tr>
<tr>
<td>Number of pills you take once a day</td>
<td>2 Kg</td>
</tr>
<tr>
<td>Number of pills you take twice a day</td>
<td>5 Kg</td>
</tr>
<tr>
<td>Personal cost to you each monthb</td>
<td>€0</td>
</tr>
</tbody>
</table>

HbA1c: glycated haemoglobin.

a In the Swedish version of the survey, HbA1c levels were converted to MonoS Standard and costs were converted to Swedish kronor.

b Based on total number of pills taken once a day only; the personal cost each month of taking pills twice a day was the total number of pills taken per day multiplied by cost per pill, based on cost and total number of pills taken once a day.
shows an example of a hypothetical choice question. In addition to the choice questions, the survey instrument also included questions on the patients’ demographic characteristics and their experiences with T2DM and its treatments.

### 2.3. Survey-testing

Semi-structured face-to-face 1 h interviews were conducted to test the survey instrument in a convenience sample of 14 patients with T2DM who were taking OAMs in Raleigh, NC, USA. In particular, these interviews aimed to test the clarity of the survey instrument, to confirm that the six attributes were important to patients and that no salient attributes had been omitted, and to assess whether patients were willing to accept trade-offs among the six attributes. Once the survey was finalized in English, the survey was translated into Swedish and German; the translated instrument was then tested on five patients in Lund, Sweden, and five patients in Berlin, Germany, to verify the translations and allow any necessary cultural adaptations before fielding the online survey to the full sample.

### 2.4. Experimental design

The combination of attribute levels included in each hypothetical medication profile was determined by a main-effects D-efficient experimental design, generated using SAS version 9.2 software [17,18]. The experimental design was restricted to include feasible combinations of attribute levels within each choice question, with treatment choices framed as decisions of whether to take a hypothetical medication once a day vs twice a day. The profile labelled “Twice a day” always had a better level of glucose control compared with the profile labelled “Once a day” (Fig. 1), but levels of each medication-related side-effect (frequency of mild-to-moderate hypoglycaemia, severe hypoglycaemic event and weight gain) were either equivalent or worse in the “Twice a day” profile. The cost per pill was the same in both profiles on the assumption that it was the same medication that only differed in frequency between the two profiles.

The experimental design resulted in 72 choice questions, which were divided among nine survey versions of eight choice questions each, and the patients were randomly assigned to one survey version. One randomly selected question was repeated for each patient for a total of nine choice questions.

### 2.5. Study sample and data collection procedures

Patient preferences for OAM outcomes were estimated for patients living in Germany and Sweden. To be included in the study, respondents had to be aged 18 years and above, have a self-reported physician’s diagnosis of T2DM and be currently taking an OAM. Potential respondents were recruited from an online consumer panel maintained by Knowledge Networks (KN), a survey research company. The panel members agreed to complete the surveys in return for KN points that could be used to redeem merchandise. This was the most cost-effective solution for data collection for this study.

In January 2012, potential respondents were sent an email inviting them to participate in the study; those who
chose to participate accessed the self-administered online survey from a personal computer. The respondents were first screened to ensure that they met the inclusion criteria. Eligible respondents were informed of the potential benefits and risks of participation in the study, and provided their informed consent before completing the 25-min survey. Before the survey was fielded, ethical issues related to the study design were reviewed by the Office of Research Protection and Ethics at RTI International (Research Triangle Park, NC) and approved by the Institutional Review Board of RTI International to ensure that the study met the ethical guidelines for survey administration in Sweden and Germany.

2.6. Statistical analysis

The bivariate probit model estimates two decisions simultaneously while recognizing the implicit correlation between the decision to accept trade-offs between convenience and other treatment attributes, and determining the relative satisfaction of each attribute level. The first decision was the willingness to trade convenience for better efficacy (patient chose “Twice a day” at least once in the sequence of choice questions) based on demographics (age, body mass index, annual household income) and treatment-experience characteristics (patient did not know their most recent HbA1c level, had a severe hypoglycaemic event since starting treatment, gained more than 5 kg in the first year since starting treatment, was currently taking an OAM once a day, strongly agreed that their treatment goal was to lower HbA1c levels and avoid side-effects, thought their risk of heart attack and stroke was higher than a person without T2DM, and exercised at least twice a week). The second decision was which attribute levels, if a patient was willing to trade, were most pertinent to making a decision (Table 1).

For each attribute, a effects coding system (1, 0, −1 for a three-level attribute instead of a dummy coding 1, 0, 0) was used to estimate a parameter for each attribute level [19,20]. With this system, the omitted categories were estimated as the negative sum of the included categories [16,21], making the mean effect of the model zero. The standard errors for each omitted category were also estimated using the variance–covariance matrix. Parameter estimates for the treatment attributes from the model can be interpreted as the relative strength of preference (preference weight) for each attribute level [8,21]. The distance between the preference weights for the best and worst levels (the difference in model coefficients) of an attribute can be interpreted as the overall mean relative importance of that attribute over the specific ranges presented in the survey [11]. In addition, subgroup analyses were also performed of each country’s sample by weight, gender, age and employment status. It should be noted that, as the study was not designed to perform these subgroup analyses, it might not have had the sample size needed in each subgroup to detect statistically significant differences. Nevertheless, it was deemed useful to look for any potential differences in preferences among the various subgroups if possible.

3. Results

3.1. Study sample and response rate

KN invited 19,063 panel members in Germany and 22,605 in Sweden to participate in the survey. Of those invited, 603 in Germany (3.2%) and 2165 in Sweden (9.6%) responded. The response rate was low because the invitation was sent to many panel members whose T2DM status was unknown. Of those who responded, 200 (33%) in Germany and 200 (9%) in Sweden were eligible to participate, based on inclusion criteria, and completed the survey and answered all nine choice questions. Table 2 summarizes the demographic and treatment-experience characteristics of these patients by country and for the overall sample. Statistically significant differences between countries included age, employment, recently switched medication, perceived treatment efficacy, mean patient’s weight and dosing requirements. The final sample size used for the analysis was 188 in Sweden and 195 in Germany, based on internal validity test results. As there were statistically significant differences in preferences between the two countries according to statistical tests, the preference weights are reported here by country. In addition, subgroup analyses performed on each country’s sample by weight, gender, age and employment status yielded no significant findings.

3.2. Preference weights for Sweden

Supplementary data, Fig. S1 presents the preference weights for Sweden. The vertical lines extending from each preference weight indicate the 95% confidence interval (CI) around the mean estimate. If the CIs between adjacent levels of a single attribute do not overlap, the mean estimates are statistically different from each other at a 5% level of significance. As demonstrated in Supplementary data, Fig. S1, the preference weights for the two levels (“Need some control” and “Need a lot more control”) of blood glucose control once a day were statistically different from each other ($P < 0.05$), but the preference weights for the two levels of number of pills taken once a day were not ($P > 0.05$). However, better clinical outcomes should logically be preferred to poorer clinical outcomes, so “Need some control” should be better than “Need a lot more control” for blood glucose control, and a 2-kg weight gain should be preferable to a 5-kg weight gain, all other things being constant. Yet, there was a slight disordering of preference weights for frequency of monthly mild-to-moderate hypoglycaemia, with the preference weight for four events being higher than the preference weight for two events. However, this anomaly was not statistically significant ($P > 0.05$).

Within each attribute, the vertical distance between adjacent preference weights indicates the relative importance of moving from one level of an attribute to an adjacent level of that attribute [11]. In our Swedish sample, improvement in blood glucose control once a day from “Need a lot more control” to “Need some control” had a relative importance of 0.4. Likewise, an improvement in weight gain from 5 kg to 0 kg had a relative importance of 0.6. Thus, the reduction in weight gain from 5 kg
to 0 kg was 1.5 times more important than the improvement in blood glucose control once a day when moving from “Need a lot more control” to “Need some control”, a result that does not reflect a logical preference for comparatively better clinical outcomes. However, this anomaly in preference weights was again not statistically significant (P > 0.05).

For our patients in Germany, an improvement in blood glucose control once a day from “Need a lot more control” to “Need some control” had a relative importance of 0.3. Likewise, an improvement in weight gain from 5 kg to 0 kg had a relative importance of 0.7. Thus, the reduction in weight gain from 5 kg to 0 kg was 2.3 times more important than improvement in blood glucose control once a day when moving from “Need a lot more control” to “Need some control”. Overall in terms of mean relative importance, the most important attribute was annual weight gain out of the range of attributes included in this study. The other attributes, ranked in decreasing order of importance, were blood glucose control once a day, the number of pills taken twice a day, annual severe hypoglycaemic event, blood glucose control twice a day, the number of pills taken once a day and frequency of monthly mild-to-moderate hypoglycaemia.

### 3.3. Preference weights for Germany

Supplementary data. Fig. S2 presents the preference weights and 95% CIs for Germany. German patients preferred better blood glucose control once a day (P = 0.01), no severe hypoglycaemic event to one severe hypoglycaemic event per year (P = 0.05), and no weight gain to a 2-kg weight gain (P < 0.05) and a 2-kg weight gain to a 5-kg weight gain per year (P < 0.05); they also preferred one pill in the morning and one pill in the evening to two in the morning and two in the evening (P < 0.05).

There were no significant differences between preferences for the other attributes.

In these patients, there was a disordering of preference weights for the following attributes: blood glucose control twice a day; frequency of monthly mild-to-moderate hypoglycaemia; and the number of pills taken once a day. For the blood glucose control twice a day attribute, the estimated preference weight of the “Controlled” level was less than that for “Need some control”, a result that does not reflect a logical preference for comparatively better clinical outcomes. However, this anomaly in preference weights was again not statistically significant (P > 0.05).

### 4. Discussion

The respondents in our sample of patients in Sweden and Germany with T2DM who were currently taking an OAM made trade-offs for efficacy (blood glucose control), tolerability (frequency of monthly mild-to-moderate hypoglycaemia, annual severe hypoglycaemic event, annual weight gain) and convenience (number of pills taken), according to our DCE. In our
two-country sample, the most important treatment attributes were weight gain followed by blood glucose control. Jendle et al. [22] reported that patients with T2DM in Sweden placed the highest value on weight loss and avoiding nausea. Porzsolt et al. [23] confirmed that weight loss was as important to patients and physicians in Germany as improvement in blood glucose control. Hauber et al. [11] found that glucose control was the most important outcome affecting patients’ medication choices, while weight gain had a significant effect on the likelihood that patients with T2DM in the United States and United Kingdom would miss or skip doses of their OAMs. One possible explanation for this consistent finding regarding the importance of weight changes in these preference studies is that patients believe that, in the long-term, weight gain will worsen blood glucose control and other diabetes-related health factors, such as cardiovascular risk. Another possible explanation is that patients believe the cosmetic impact of weight gain may outweigh the health benefits of better glucose control. Indeed, Matza et al. [24], using Standard Gamble methods, found that body mass index had a direct negative effect on drug use among T2DM patients in Scotland and England.

As described above, the importance of reductions in weight gain versus improvement in moderate blood glucose control was greater for German patients than Swedish ones. These results suggest that better blood glucose control was more important to Swedish patients than German patients. However, this finding could not be formally tested, as the data for the two countries could not be pooled based on statistical tests. Also, this finding may be due to the fact that blood glucose control guidelines are stricter in Sweden than in Germany. An alternative explanation is that the differences in baseline characteristics, where the German patients were heavier, may have led to their stronger preferences for weight neutrality or weight reduction.

Our results have demonstrated that the attribute of mild-to-moderate hypoglycaemic events was the least important to both Swedish and German patients. This result appears to be contradictory to other studies [25]. However, our survey patients were informed of the symptoms of mild-to-moderate hypoglycaemia and told that it could be managed with orange juice or a snack. Also, our patients in their pretest interviews confirmed that this was not a major concern when making treatment decisions, as many patients had experienced one or more such events and so typically carried juice or snacks with them on a daily basis just in case. Despite the fact that there were differences in the patients’ baseline characteristics between the two countries, there was no systematic relationship between these differences and differences in preferences between the two national groups.

Our present study demonstrated that patients made trade-offs for efficacy, tolerability and convenience of OAMs, but there were some limitations. First, patients evaluated hypothetical medications, and differences may arise between stated and actual choices. However, making the hypothetical choices mimic real-world trade-offs as closely as possible minimized the possibility of bias, and the attributes included in the survey were verified during pretest interviews. Second, the response rate for this study was low (<10%) in both Sweden and Germany, which may have introduced a selection bias. In addition, there are no data for the characteristics of non-respondents, of respondents who failed to meet the inclusion criteria and of those who did not consent to participate. Thus, it cannot be determined whether the recruitment procedure used in this study resulted in selection bias. However, the recruitment procedure was cost-effective and reduced the burden of the survey in terms of the respondents’ time and effort, as the survey could be completed at home on a personal computer, thereby, also making it possible to meet the study’s timelines. Finally, the mean age of the respondents in our sample and their employment rates were lower than that seen in a typical diabetes population. For these reasons, it is advisable to use caution when generalizing these results to all patients with T2DM in Sweden and Germany. In conclusion, in this patient preference survey, the avoidance of weight gain was the most important attribute for OAMs in both countries.

Disclosure of interest

Drs Duprat Lomon and Malvolti are employees of Bristol-Myers Squibb and have stock ownership; Dr Townsend is an employee of AstraZeneca and has stock ownership.

The other authors declare that they have no conflicts of interest concerning this article.

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Appendix A. Supplementary data

Supplementary data (Figs. S1 and S2) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabet.2013.06.001.

References


