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Patient preferences for anti-hyperglycaemic medication for type 2 diabetes mellitus in China: findings from a national survey

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ABSTRACT

Objective This study aimed to investigate the preferences regarding risks, benefits and other treatment attributes of patients with type 2 diabetes mellitus (T2DM) in China when selecting a second-line anti-hyperglycaemic medicine.

Methods A discrete choice experiment with hypothetical anti-hyperglycaemic medication profiles was performed using a face-to-face survey administered to patients with T2DM. The medication profile was described using seven attributes: treatment efficacy, hypoglycaemia risk, cardiovascular benefits, gastrointestinal (GI) adverse events, weight change, mode of administration and out-of-pocket cost. Participants chose between medication profiles by comparing attributes. Data were analysed using a mixed logit model with marginal willingness to pay (mWTP) and maximum acceptable risk (MAR) calculated. The preference heterogeneity within the sample was explored using a latent class model (LCM).

Results A total of 3327 respondents from five major geographical regions completed the survey. Treatment efficacy, hypoglycaemia risk, cardiovascular benefits and GI adverse events were major concerns among the seven attributes measured. Weight change and mode of administration were of lesser concern. Regarding mWTP, respondents would pay ¥236.1 (US$36.6) for an anti-hyperglycaemic medication with an efficacy of 2.5% points reduction in HbA1c, while they were willing to accept a weight gain of 3 kg only if they received a compensation of ¥56.7 (US$8.8). Respondents were willing to accept a relatively large increase in hypoglycaemia risk (MAR=15.9%) to improve treatment efficacy from intermediate (1.0% points) to high (1.5% points). LCM identified the following four unobserved subgroups: trypanophobia, cardiovascular-benefits-focused, safety-focused and efficacy-focused and cost-sensitive.

Conclusion Patients with T2DM prioritised free out-of-pocket costs, highest efficacy, no hypoglycaemia risk and cardiovascular benefits over weight change and mode of administration. There exists great preference heterogeneity among patients, which should be taken into account in healthcare decision-making processes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The clinical decision to choose one anti-hyperglycaemic medication over another is complex and should be guided by a patient-centred approach, in which patient preferences should be included.

⇒ The preferences for anti-hyperglycaemic medications of Chinese patients with type 2 diabetes mellitus are still unknown.

WHAT THIS STUDY ADDS

⇒ Out-of-pocket cost, treatment efficacy, hypoglycaemia risk, cardiovascular benefits and gastrointestinal adverse events were major concerns among the seven attributes measured. Weight change and mode of administration were of lesser concern.

⇒ We identified the following four unobserved preferences heterogeneity subgroups: trypanophobia, cardiovascular-benefits-focused, safety-focused and efficacy-focused and cost-sensitive.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides information on which anti-hyperglycaemic medication characteristics are most important from a patient perspective and shows that patients demonstrate heterogeneity in their medication preferences.

⇒ Recognising that patients will make different trade-offs when choosing one treatment over another can improve the healthcare decision-making processes and promote a patient-centred diabetes care.

INTRODUCTION

The prevalence rate of diabetes in China increased from less than 1% in the 1980s to more than 12% in 2018.[1 2] In 2021, China was reported to have the largest number of patients with diabetes and the second highest healthcare spending on diabetes and its complications worldwide.[3–5] Previous research showed lower rates of awareness, treatment and control of diabetes in China compared with the USA.[3 6 7] Type 2 diabetes

mellitus (T2DM) is a complex chronic illness requiring continuous medical care including multifactorial risk-reduction strategies beyond glycaemic control.

Established guidelines recommend that once initiated, metformin should be continued as long as it is tolerated and not contraindicated.[8] However, given the progressive nature of the disease, within 3 years of receiving monotherapy, 50% of patients with T2DM are inadequately controlled and require add-on therapies.[9] The American Diabetes Association highlights that the choice of medication added to metformin should be based on the clinical characteristics of the patients and their preferences.[8] For patients with established atherosclerotic cardiovascular disease (ASCVD) or indicators of high ASCVD risk, heart failure (HF) or chronic kidney disease (CKD), a sodium-glucose cotransporter-2 inhibitor (SGLT2i) or glucagon-like peptide-1 receptor agonist (GLP-1 RA) with demonstrated cardiovascular disease (CVD) benefits is recommended. For patients without the above indicators, the choice of a second agent to add to metformin is not yet guided by empirical evidence comparing across multiple classes.[8] Rather, drug choice is based on efficacy, avoidance of side effects (hypoglycaemia or weight change), cost and patient preferences. For example, if the main driver of the treatment choice is out-of-pocket cost, a sulphonylurea or thiazolidinedione (TZD) might be considered because these drugs are currently reimbursed in China; if the main concern is to avoid hypoglycaemia, GLP-1 RAs, SGLT2i, dipeptidyl peptidase IV inhibitor (DPP-4i) or TZD might be preferred.[10]

In accordance with the national guidelines for the prevention and control of diabetes in primary care in China, patient preference is an important consideration in the formulation of individualised treatment plans.[11] The US Food and Drug Administration released a guide in 2016 that encourages the use of data on preferences of patients and caregivers in medical product development.[12] Discrete-choice experiment (DCE) is an effective approach used since before 1990 to quantify the preferences of patients regarding healthcare and a wide range of related topics.[13]

Several DCEs have been conducted in the European and American diabetes population.[14] However, nationally representative Chinese patient preferences have not been investigated. Conclusions from previous studies conducted outside China may not be generalisable to Chinese patients because of inconsistent results and different cultural contexts between China and high-income countries. Huang *et al*[15] investigated the treatment preferences of patients with T2DM in China but did not consider their medication preferences and only enrolled participants in the hospital setting. However, a large proportion of patients with T2DM are in the primary healthcare setting, such as, those patients who are living in rural areas.[2 16]

Therefore, the present study used the DCE as a patient decision aid aiming to bridge research gaps by identifying the preferences regarding risks, benefits and other treatment attributes of patients with T2DM in China when selecting a second-line anti-hyperglycaemic medicine. Findings from this study may provide empirical evidence for clinicians or policymakers on how to choose an optimal therapy among multiple suitable alternative medications for patients with T2DM, thus improving medication adherence and promoting a patient-centred diabetes care.

METHODS

Patient and public involvement

Patients were involved in the design, conduct, reporting or dissemination plans of our research.

Study sample

In China, there are regional variations in the prevalence of diabetes,[16] and different geographical regions have different levels of economic development, which may have an impact on a patient's medication choices. As such, we used a multistage stratified cluster-sampling procedure that considers geographical region and economic development status for data collection. In stage one, we selected six provinces and municipalities that represent the socioeconomic statuses and lifestyles of five major geographical regions in China. In stage two, we selected a provincial capital city (developed city) and one or two non-provincial capital cities (underdeveloped city) from each geographical region in China. In stage three, we randomly selected one or two hospitals and two or three primary care institutions from each city. Finally, we selected 50 hospitals or primary care institutions from 13 cities in 5 provinces and 1 municipality. Participants were eligible to complete the survey if they were Chinese, ≥18 years of age and diagnosed with T2DM by a healthcare professional. Individuals were asked to participate regardless of their medication history.

The guidelines proposed by Johnson and Orme suggested that the sample size can be calculated using the equation $N>500\times c/(t\times a)$, where c indicates the number of analysis cells, t refers to the number of choice tasks and a is the number of alternatives. In the main-effects only design, c is equal to the largest number of levels among different attributes in the DCE.[17] In the present study, the corresponding values for c, t and a are 6, 6 (exclude the duplicated choice set) and 2, respectively; therefore, N can be estimated as $(500\times6)/(6\times2)=250$. To conduct preference heterogeneity analyses, we set the sample size for each geographical region as no less than 250, and the total sample was no less than 1250.

Attributes and levels development

A range of medications in oral and/or injectable form are available to control blood glucose. This variety of treatment options naturally provides a diversity of clinical efficacy, administration mode and adverse event profiles. An initial list of attributes was obtained by conducting a review of the published literature.[8 10 14 18] Each initial attribute was then subjected

to multiple rounds of prioritisation following three principles: relevance to the research question, relevance to the decision context and whether attributes are related to one another. This procedure yielded 13 attributes. Subsequently, an expert stakeholder panel consisting of five endocrinologists and three administrators in diabetes care was convened to refine the attribute list and identify possible gaps. In this stage, we combined the attributes 'nausea', 'vomit' and 'diarrhea' into 'gastrointestinal (GI) adverse events' and defined the cost as 'monthly out-of-pocket cost'. We then conducted a best-worst scaling (BWS) experiment involving 362 patients with T2DM. This experiment is an effective priority determination method that can provide quantitatively robust evidence for the DCE attribute selection and helped us to refine the 11 attributes (online supplemental table 1) generated from the literature review and the first-stage expert consultation. The BWS results provided a clear view of the priority of the 11 attributes. Details of the BWS results can be found in the study by Liu *et al*.[19] These attributes were further refined through focus-group discussions with six endocrinologists in Shanghai, China.

Based on the literature review, expert consultation, BWS results and focus-group interview, seven attributes were included in the final survey. The levels of treatment efficacy,[8 10 20 21] weight change,[10 22] hypoglycaemic risk[8 10 23 24] and GI adverse events[8 10 25–27] were mainly determined by randomised controlled trials, systematic reviews and clinical guidelines focused on the efficacy and safety of medication treatments for patients with T2DM. We also reviewed the package inserts of anti-hyperglycaemic medicines that were available to Chinese patients. To reduce the cognitive burden of participants, the levels of the 'cardiovascular benefits' attribute were qualitatively identified with 'yes' and 'no' to represent whether the anti-hyperglycaemic medications can provide cardiovascular benefits or not.[8 10] The levels of the 'monthly out-of-pocket cost' attribute were determined by analysing the health insurance data obtained from one tertiary hospital and experts interview. Considering the Chinese context, ¥0 represented the nearly free anti-hyperglycaemic medications, such as sulphonylureas and biguanides, whereas ¥600 represented the expensive anti-hyperglycaemic medications, such as insulin therapy and some GLP-1 RA (table 1).

Experimental design

The final set of DCE questions included in the survey was generated with a commonly used D-optimal algorithm by SAS to construct a fractional factorial experimental design. The resulting design included 48 unique DCE questions, which were assembled into 8 blocks of 6 DCE questions each. The final experimental design was evaluated for level balance, minimal overlap and orthogonality. The aim of this type of experimental design is to strike a balance between asking enough DCE questions of each respondent to estimate the model parameters for each attribute level while not overburdening the respondent with too many questions. Each respondent was randomly assigned to answer one of the blocks of six questions. Each DCE question offered respondents a choice between two hypothetical medication profiles, and patients were asked which medication they would prefer to choose. Within each block, a strictly dominant option (alternative A is preferred over alternative B) was included to evaluate the internal validity of the data. After the DCE questions, the surveys contained additional questions about demographic information, such as duration of diabetes and current medication use. The design was developed following good research practice guidelines published by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).[28]

Data collection

To ensure the quality of data collection, we collected the data in a face-to-face manner. In the tertiary hospitals, the questionnaire was administered to patients by clinicians and the research team. In the primary care institutions, the face-to-face survey was conducted in a conference or waiting room by the research team. The instructions of the DCE and the rationale of the survey were explained in detail by one or two investigators who received specific training from the research team.

Cognitive pre-tests were conducted to ensure the face validity of the survey instrument and comprehensibility of the survey method. We conducted iterative pre-tests on paper (n=5) and, after revisions, conducted additional pre-tests in an online format (n=7). Respondents were provided pre-test questions and were given the option to verbally share comments during the pre-test. The patients completed the questionnaire themselves anonymously after they provided informed written consent. Respondents who had difficulty filling in the questionnaire—for example, those who had poor eyesight—were offered the opportunity to complete the questionnaire verbally. The completion of the questionnaire took about 10–20 min, and each participant was reimbursed for their time. All completed questionnaires were directly returned to the investigators.

Statistical analysis

We fitted the DCE data to a conditional logit model (CLM) and mixed logit model (MIXL) using dummy coding. The optimal model was chosen by examining the Bayesian information criterion (BIC) and Akaike information criterion (AIC). The signs of coefficients of the model indicated whether the corresponding attributes had a positive or negative effect on utility, and the sizes of the coefficients indicated the attributes' relative importance based on total relative utility.

Table 1 Attributes and levels in the discrete-choice experiment survey

Attributes	Levels	Description	Some corresponding medications
Treatment efficacy/ reduction in HbA1c	Highest/2.5%	Different diabetes drugs have different efficacies for reducing the HbA1c	Insulin
	High/1.5%		Insulin, GLP-1 RA, SGLT-2i
	Intermediate/1.0%		Sulfonylureas, nateglinide, biguanides
	Poor/0.5%		TZD, alpha-glucosidase inhibitor, DPP-4i
Hypoglycaemic risk	0%	The likelihood that patients will experience mild or moderate hypoglycaemic events within the first 6 months of use	TZD, alpha-glucosidase inhibitor
	5%		Nateglinide
	15%		Sulfonylureas
	30%		Insulin
Gastrointestinal adverse events	0%	The likelihood that the medication will cause any mild or moderate GI adverse events (which may include diarrhoea, vomiting and/or nausea) within the first 6 months of use.	DPP-4i, SGLT-2i
	10%		Meglitinide
	20%		alpha-glucosidase inhibitor
	40%		GLP-1 RA
Cardiovascular benefits	Yes		GLP-1 RA, SGLT-2i
	No		Others
Weight change	–2 kg	Medication-related weight changes that patients will experience within the first 6 months of use.	SGLT-2i, GLP-1 RA
	0 kg		DPP-4i, alpha-glucosidase inhibitor
	+1.5 kg		Sulfonylureas, nateglinide, TZD
	+3 kg		Insulin
Mode of administration	Injection	--	Insulin, most GLP-1 RA
	Pill		Others
Out-of-pocket cost*	¥0	Patients' monthly out-of-pocket cost.	Sulfonylureas, glucosidase
	¥50		TZD, nateglinide
	¥100		alpha-glucosidase inhibitor
	¥200		DPP-4i,SGLT-2i
	¥400		Most insulin
	¥600		Some insulin, GLP-1 RA

*Based on a currency exchange rate of ¥6.449 to US$1.00 in 2021.
.DPP-4i, dipeptidyl peptidase IV inhibitor; GI, gastrointestinal; HbA1c, glycated haemoglobin A1c; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium-glucose cotransporter two inhibitor; TZD, thiazolidinedione.

The cost attribute was assumed to be continuous. Thus, the marginal willingness to pay (mWTP) was calculated by assessing the ratio of the preference for other attributes to the preference for out-of-pocket cost.

There is a sensitive trade-off between glucose control and hypoglycaemic risk in patients with T2DM in medication.[8] Thus, in our study, in addition to preference weights for attributes, the risk tolerance, that is, the hypoglycaemic risk accepted by patients with T2DM to achieve an incremental glucose control benefit, was quantified using the maximum acceptable risk (MAR) introduced by Johnson *et al*.[29] MAR expresses the risk patients are willing to take to gain a certain amount of benefit. The MAR is theoretically higher if the benefits produced by the intervention increase. Quantitative estimates of MAR can provide useful information for several areas of product development and marketing, such as development strategies for new pharmaceuticals, regulatory approval and risk management.

We conducted a latent class analysis (LCA) to assess the presence of structural differences in the ranking of preferences within the sample (ie, preference heterogeneity). This method tests the presence of unobserved (latent) classes within the sample based on a set of variables that define each observation—in this case, patient preferences for anti-hyperglycaemic medication attributes. Within each class, preference weights were estimated using a CLM.[30] A user-written Stata module,[31 32] lclogit, was used to conduct this analysis. Demographics for each class were tabulated using by class: tabulate in Stata after model estimation. We fitted the data to one to six classes and used the BIC and AIC to choose the model with the best goodness-of-fit. All statistical analyses were conducted using Stata statistical software.

RESULTS

A total of 3919 respondents met the eligibility criteria and consented to participate. Of those who consented to participate, 3533 completed the survey (90.2%). Some respondents were excluded for failing the internal validity test (n=206), leaving 3327 respondents for the final analysis ; there were no statistically significant differences in demographic characteristics between those who failed versus those who passed the validity test (online supplemental table 2). Among the participants, 50.8% were women, 63.9% lived in urban areas, 50.0% had a body mass index (BMI) ≥24 and 55.8% were more than 60 years old, which is consistent with the estimated prevalence of diabetes among Chinese adults, making the sample broadly nationally representative.[2]

Approximately 65.2% of respondents had been diagnosed with diabetes for at least 5 years, and 65.1% took at least two medications for diabetes. In addition, 18.0%, 11.8% and 8.6% of respondents were diagnosed with a CVD, CKD and HF, respectively. Most of the respondents indicated having a clear understanding of the harmful effects of diabetes on their health. More than half of the respondents (65.3%) considered that the six DCE tasks were of average difficulty (neither easy nor difficulty) to complete. The number of respondents in each block had a good balance (11.6% to 13.4%).

Preference weight

The AIC and BIC values suggested that the MIXL outperformed the CLM (online supplemental table 3), and the preferences results were not substantially different between the two models. Table 2 shows the MIXL results of the participants who passed the internal validity test (39 924 observations from 3327 patients). A sensitivity analysis involving the 206 participants who failed the internal validity test was conducted (online supplemental table 4), although these changes did not substantially affect the findings. Except for a weight change of

Table 2 Mixed logit model for respondent preferences

Attributes/levels	Estimate	SE	P value	SD	SE	P value
Efficacy/reduction in HbA1c: 0.5% (ref.)						
1.0%	0.583	0.062	<0.001	0.066	0.255	0.795
1.5%	1.256	0.081	<0.001	0.431	0.185	0.020
2.5%	1.378	0.082	<0.001	0.912	0.123	<0.001
Hypoglycaemia events risk: 30% (ref.)						
15%	0.810	0.068	<0.001	0.030	0.125	0.809
5%	1.175	0.073	<0.001	0.321	0.243	0.187
0%	1.271	0.078	<0.001	0.779	0.134	<0.001
Gastrointestinal adverse events: 40% (ref.)						
20%	0.417	0.060	<0.001	0.029	0.266	0.914
10%	0.608	0.066	<0.001	0.344	0.200	0.086
0%	1.138	0.078	<0.001	1.270	0.112	<0.001
Weight change: no change (ref.)						
−2 kg	0.098	0.067	0.142	0.108	0.244	0.657
+1.5 kg	−0.197	0.059	0.001	0.314	0.228	0.170
+3 kg	−0.331	0.069	<0.001	0.987	0.113	<0.001
Cardiovascular benefits: no						
Yes	1.172	0.060	<0.001	1.243	0.075	<0.001
Mode of administration: injection (ref.)						
Pill	0.913	0.056	<0.001	1.451	0.080	<0.001
Cost	−0.0058	0.000	<0.001	0.006	0.000	<0.001
Constant	−0.101	0.036	0.006	--	--	--
n	3327					
Observation	39 924					
Log-likelihood	−10 277.503					
AIC	20 617.010					
BIC	20 883.440					

.AIC, Akaike information criterion; BIC, Bayesian information criterion; HbA1c, glycated haemoglobin A1c.

−2 kg, all levels within each attribute were statistically different from one another at the 1‰ level, suggesting that the selected attributes were all significant predictors of patient medication choice. The participants particularly cared about treatment efficacy, strongly favouring a 2.5% point reduction in glycated haemoglobin A1c (HbA1c) (β=1.378; p<0.001). They also exhibited strong preferences for a medication without hypoglycaemia risk over one with a 30% risk (β=1.271; p<0.001), and for a medication with cardiovascular benefit over one without (β=1.172; p<0.001). The attribute GI side effects (β=1.138; p<0.001) was in the middle rank and had significant impact.

Other attributes had less influence on respondent choice than did the four described above. The respondent choice was not greatly influenced by administration mode or weight change, although certain levels of each of the two attributes had positive or negative effects on respondent choice. For example, weight gain had a negative effect on the medication preferences of patients with T2DM, but to a lesser extent. The relative preference weight for a weight change of +3 kg was only less than one-third of the 2.5% point reduction in HbA1c. The 'out-of-pocket cost' attribute, treated as continuous, was −0.0058. Thus, every 100 additional yuan spent on the anti-hyperglycaemic medication decreased the patient's utility by 0.58.

MWTP

The mWTP analysis quantified the monetary equivalence that the respondents were willing to sacrifice for the desired level of an anti-hyperglycaemic medication attribute compared with the reference level. mWTP estimates are depicted in figure 1. Respondents were willing to pay ¥215.2 (US$33.4) for an anti-hyperglycaemic medication with an efficacy of 1.5% point reduction in HbA1c over one with an efficacy of 0.5% point reduction in HbA1c. However, respondents were willing to pay only another ¥20.9 (US$ 3.2) to obtain an additional 1.05% point reduction in HbA1c. They were also willing to pay ¥217.7 (US$33.8) for a medication with 0% hypoglycaemia risk over one with a 30% risk, ¥200.7 (US$31.1) for a medication with cardiovascular benefits over one without such benefits and ¥194.9 (US$30.2) for a medication without GI risk over one with GI risk. Respondents were willing to pay ¥−56.7 (US$−8.8) for a weight change of +3 kg over their current weight. In other words, they were willing to accept a weight gain of 3 kg when compensated with ¥56.7.

MAR

The MAR results are illustrated in figure 2. For a specified improvement in treatment efficacy (Δefficacy), MAR is the highest level of hypoglycaemia risk patients would tolerate in return for a reduction in HbA1c offered by the anti-hyperglycaemic medication. Patients were willing to accept a relatively large increase in hypoglycaemia risk (MAR=15.9%) to improve treatment efficacy from intermediate (1.0% point) to high reduction (1.5% point), closely followed (MAR=13.8%) by an improvement from poor (0.5% point) to intermediate reduction (1.0% point); however, they would only accept a small increase in risk (MAR=2.8%) from high (1.5% point) to highest reduction (2.5% point).

Preference heterogeneity

The LCA results showed that four classes were the best fit for these data (table 3 and online supplemental table

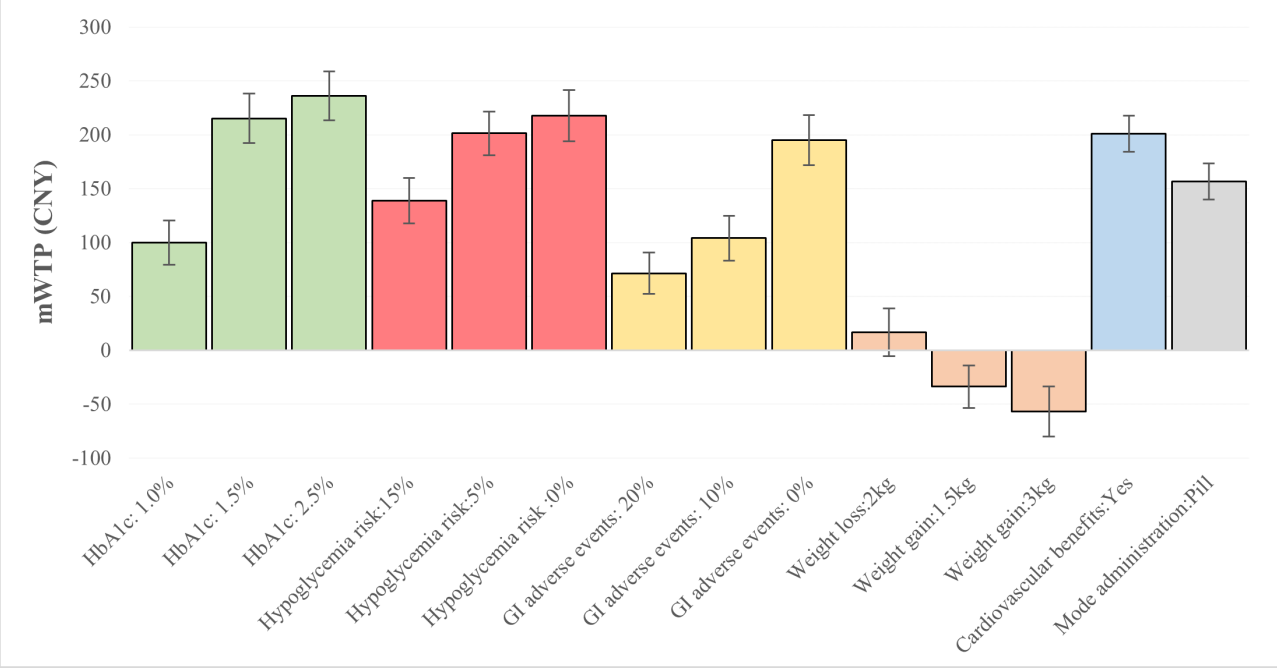

Figure 1 Marginal willingness to pay. Based on a currency exchange rate of ¥6.449 to US$1.00 in 2021. GI adverse events, gastrointestinal adverse events; HbA1c, glycated haemoglobin A1c; mWTP, marginal willingness to pay.

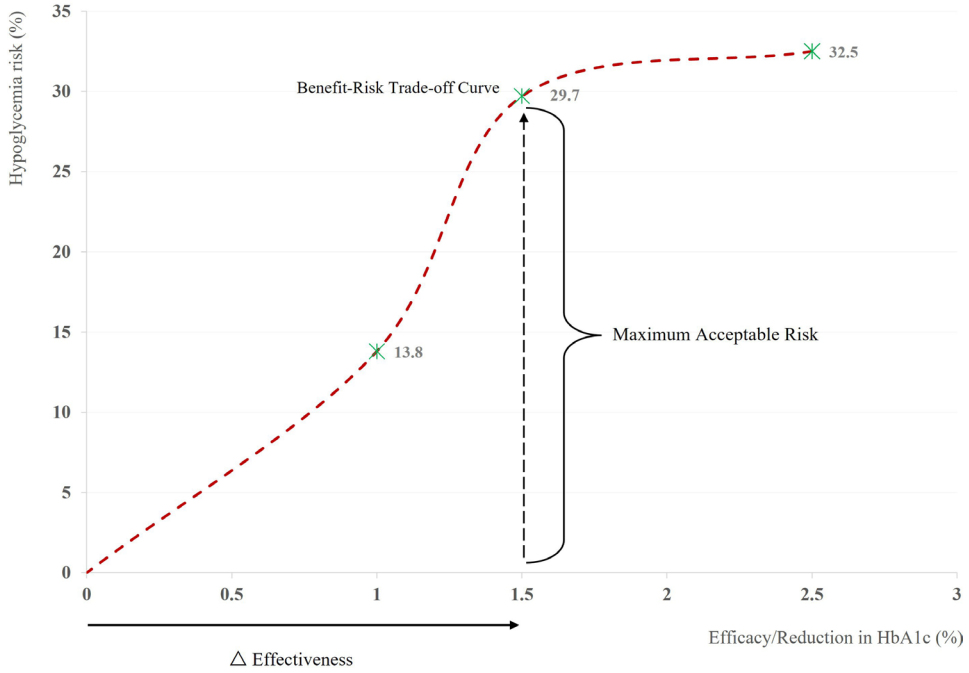

Figure 2 Benefit-risk trade-off curve and maximum acceptable risk. HbA1c, glycated haemoglobin A1c.

5). The first class 'trypanophobia', which included 359 respondents (10.8%), strongly preferred oral administration. Those 1065 respondents (32.0%) in the second class 'cost sensitive' were most sensitive to out-of-pocket costs. The third class 'cardiovascular-benefits-focused', which was composed of 739 respondents (22.2%), was most concerned with cardiovascular benefits. The fourth class 'safety-and efficacy-focused' was the largest, composed of 1164 respondents (35.0%) who were primarily concerned with treatment efficacy, hypoglycaemia risk and GI adverse events. When assessing demographic characteristics, those without injection therapy experience were more likely to be grouped in class 1 than those with such experience. Respondents from urban areas or with higher education levels were less likely to belong to class 2. Class 3 was more likely to include urban respondents and those with a BMI ≥24. Older inpatients with higher education levels had a higher probability to be classified into class 4 than their counterparts.

DISCUSSION

To the best of our knowledge, this study is the first to investigate the preferences of patients with T2DM regarding second-line anti-hyperglycaemic medications by performing a DCE with a nationally representative sample in China. For the clinician or decision-maker, our study provides robust evidence on the relative importance to patients of factors that likely influence their treatment decision-making related to medications for T2DM. T2DM is a particularly preference-sensitive condition because of the multitude of available treatments, which have varied benefits, risks and burdens.[33] In this study, we estimated the relative importance of preference weight, associated mWTP, MAR and preference heterogeneity. The results showed that out-of-pocket cost, treatment efficacy, hypoglycaemia risk, cardiovascular benefits and GI adverse events were the most important attributes in patient decision-making, whereas administration mode and weight change were the least important. These preferences except for weight gain differed largely by key demographic characteristics.

Our study revealed the importance of out-of-pocket costs in patient preferences. Other studies from countries with universal health coverage, such as Canada and America, also found similar results.[34 35] Financial barriers remain a major source of health disparities, and costs should be a focus of treatment goals.[36] According to a National Health Interview Survey, one-half of adults with diabetes reported financial stress; among them, most of those who reported not taking medications as prescribed due to cost-related barriers to medication use never shared this with their physician.[37 38] Findings from the present study suggest that, in order to reduce the risk of cost-related non-adherence, the costs of care should be strongly considered by physicians in China when developing treatment plans.

Patients weighted the efficacy for a reduction in HbA1c as more important than other risks and benefits measured. These results are in line with a recent systematic review of DCE studies of patient preference in diabetes, where control of blood glucose (reflected in HbA1c) was identified as the most important attribute relating to patient preference.[39] In our study, patients were willing to pay ¥215.2 (US$ 33.4) to decrease HbA1c by 1.5% point compared with 0.5% point. However, they were only willing to pay another ¥20.9 (US$ 3.4) to decrease HbA1c from 2.5% point to 1.5% point. It suggested that patients in our study had a clear awareness

Table 3 Latent class model for preferences heterogeneity (n=3327)

	Class 1 (trypanophobia)		Class 2 (cost sensitive)		Class 3 (cardiovascular-benefits-focused)		Class 4 (safety-focused and efficacy-focused)	
Attributes/levels	**Estimate**	**P value**	**Estimate**	**P value**	**Estimate**	**P value**	**Estimate**	**P value**
Efficacy/reduction in HbA1c: 0.5% (ref.)								
1.0%	0.110	0.777	0.570	<0.001	0.331	0.003	0.707	<0.001
1.5%	0.515	0.125	0.524	<0.001	0.810	<0.001	1.173	<0.001
2.5%	0.499	0.202	0.896	<0.001	1.002	<0.001	1.197	<0.001
Hypoglycaemia events risk: 30% (ref.)								
15%	−0.278	0.498	0.348	0.024	0.099	0.304	0.947	<0.001
5%	−0.062	0.838	0.302	0.105	0.643	<0.001	1.417	<0.001
0%	−0.258	0.496	0.156	0.234	0.178	0.085	1.938	<0.001
Gastrointestinal adverse events: 40% (ref.)								
20%	−0.217	0.558	0.167	0.237	0.179	0.040	0.559	<0.001
10%	0.449	0.171	0.161	0.311	0.157	0.119	0.778	<0.001
0%	−0.016	0.961	0.712	<0.001	0.264	0.002	1.431	<0.001
Weight change: no change (ref.)								
−2 kg	−0.187	0.651	−0.159	0.330	0.095	0.360	0.099	0.298
+1.5 kg	−0.318	0.537	−0.567	<0.001	0.013	0.893	−0.262	0.005
+3 kg	−0.339	0.280	−0.618	<0.001	−0.344	<0.001	−0.358	<0.001
Cardiovascular benefits: no								
Yes	0.201	0.469	0.486	<0.001	1.569	<0.001	−0.149	0.197
Mode of administration: injection (ref.)								
Pill	3.196	<0.001	0.663	<0.001	0.172	0.008	0.302	<0.001
Cost	−0.002	0.002	−0.011	<0.001	−0.001	<0.001	−0.000	0.807
Individual covariates								
Age (year): >60	−0.320	0.050	−0.224	0.069	−0.013	0.927	–	–
Inpatient	−0.380	0.038	−0.206	0.114	0.196	0.165	–	–
Region: urban	0.151	0.422	−0.681	<0.001	0.458	0.004	–	–
Education: high school or above	−0.031	0.865	−0.595	<0.001	−0.257	0.078	–	–
Annual family income: >¥50000	0.502	0.002	0.188	0.117	0.428	0.001	–	–
BMI: ≥24	−0.132	0.405	0.164	0.164	0.220	0.098	–	–
Has no injection therapy experiences	1.794	<0.001	0.472	<0.001	0.132	0.362	–	–
Constant	−2.177	<0.001	0.863	<0.001	−0.502	0.124	–	–
Class share	0.108		0.320		0.222		0.350	

BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; HbA1c, glycated haemoglobin A1c.

of the efficacy attribute, as they perceived that higher efficacy was not necessarily better. In clinical practice, when making medication recommendations for patients, physicians must make a careful trade-off between various medicines in terms of glucose control and avoiding hypoglycaemia because when optimal glucose levels are achieved, the risk of short-term complications, such as hypoglycaemia, is expected to increase.[40 41] Our study confirmed this again, as we found that treatment efficacy and hypoglycaemia risk had a great impact on patient medication preferences and patients made a sensitive trade-off between the two attributes.

Other preference studies separated the hypoglycaemia attribute into mild and severe, which may increase the patient's trade-off burden when making a choice.[35 42] By contrast, the present study used 'risk of moderate or mild hypoglycemia events within 6 months' to define the hypoglycaemia attribute because severe hypoglycaemia did not seem to occur more often with any particular monotherapy or combination therapy.[25] Older patients

were more likely to be grouped in the safety-focused and efficacy-focused class. The strength of the preference for glucose control reflects the challenges (eg, multiple coexisting chronic illnesses and poor treatment adherence) faced by older patients to achieve such control.

Patients, particularly those with a BMI ≥24, had a high preference for cardiovascular benefits in our study. Although the use of anti-hyperglycaemic medications is generally not associated with increased cardiovascular risk, patients with diabetes, especially those with comorbid obesity, inherently have an increased risk of CVD.[43] Clinical trials showed that GLP-1 RAs have beneficial effects on cardiovascular health, but high costs are an important barrier to GLP-RA use. In the present study, the respondents were willing to pay only ¥200.7 (US$ 31.1) to take medication with cardiovascular benefits over one without, which is far below the medical cost of GLP-RA in China.[44] Thus, the government should take steps to have more GLP-RA medicines covered by the public health insurance.

Although GLP-RA has demonstrated various benefits for patients, it has the highest GI adverse events risk among anti-hyperglycaemic medications.[11 45 46] In the present study, older patients had relatively high concern for GI adverse events. Thus, in clinical practice, when recommending GLP-1 RA for older patients, a careful trade-off should be made between the benefits and potential GI adverse event risks to improve their medication adherence.

Overall, patients preferred the oral versus injection mode of administration. Several previous studies also found similar results.[47 48] The preference heterogeneity results indicated that the patients who had never had an injection preferred oral administration over injection therapy. Thus, a lack of understanding of the characteristics of injection therapy may be a potential barrier to insulin use. Another study also suggested that diabetes education can considerably influence the importance assigned to administration mode among patients with T2DM.[48]

Patient preferences were least influenced by weight change. This is consistent with a recently published double-blind, randomised three-way crossover trial study examining patient preferences for therapy in T2DM.[49] Although worry about weight gain is common among patients with T2DM, the present study suggests that Chinese patients were generally not willing to trade efficacy or safety to avoid weight gain.

Limitations

This study has some limitations. First, the attributes and their levels in the DCE survey must be formulated in such a way that respondents clearly and concisely understand their meaning. Although the levels of the treatment efficacy attribute in terms of HbA1c reduction was presented to participants using both qualitative (highest, high, intermediate and poor) and quantitative (2.5%, 1.5%, 1.0% and 0.5%) descriptions in this study, the understanding of HbA1c reduction may be problematic for some patients. Future studies are encouraged to include attributes that can be easily interpreted by the patients, such as, loss of life years.

Second, considering that DCEs are not appropriate when too many attributes are considered, we combined nausea, vomit and diarrhoea into 'GI adverse events' to prevent participant fatigue. However, we could not determine the specific preference weight between those factors. In addition, given that the burden of GI adverse events varies largely based on its severity, adopting the risk of overall GI events rather than of severe events could be another limitation of this study.

Third, we did not leave respondents an opt-out option. A forced choice design may cause some biases, but this design was consistent with our study setting. Because of the progressive nature of T2DM, medication therapy is necessary to maintain euglycaemia over time.

Fourth, an inherent limitation of the DCE design is that it requires participants to make hypothetical rather than observed choices. Stated preferences on hypothetical choices may not be reflective of reality, where patients make decisions with emotional, financial and clinical consequences.[50] Nevertheless, we attempted to minimise differences between hypothetical and real-world decision-making environments by choosing attributes and levels that are consistent with real clinical decisions. In addition, to ensure the quality of the preferences evidence, we followed recommended guidelines proposed by ISPOR for DCE study design[28] and analysis.[30] Cognitive pre-tests were also conducted to ensure the face validity of the survey instrument and comprehensibility of the survey method.

Fifth, we only collected the number of medications currently taken by the patients for diabetes. Collecting further details of medications currently taken by patients may provide deep insights regarding their medication preferences, as current medications might impact the patients' preferences for the hypothetical medicines presented in this DCE.

Finally, there may also be a limitation for the sampling procedure as we did not adopt random sampling. However, to make the preference results more representative, our study used a multistage stratified cluster-sampling procedure that considers geographical regions and economic development status for data collection. In addition, the key demographic characteristics are consistent with the estimated prevalence of diabetes among Chinese adults, making the sample broadly nationally representative.

CONCLUSIONS

The decision to choose one medication over another is complex and should be guided by a patient-centred approach. Considerations include the medication effects on cardiovascular and renal comorbidities, efficacy, hypoglycaemia risk, impact on weight, out-of-pocket

cost, risk for side effects and patient preferences. This study suggests which attributes are most important from a patient perspective and shows that patients demonstrate heterogeneity regarding medication preferences, the quantitative trade-offs further illustrate the relative importance of these attributes. Hence, the results of this study are informative and robust and can be used to guide healthcare decision-making processes for patients with T2DM.

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REFERENCES

1 Pan X-R, Yang W-Y, Li G-W, *et al*. Prevalence of diabetes and its risk factors in China, 1994. *Diabetes Care* 1997;20:1664–9.
2 Wang L, Peng W, Zhao Z, *et al*. Prevalence and treatment of diabetes in China, 2013-2018. *JAMA* 2021;326:2498–506.
3 Wang L, Gao P, Zhang M, *et al*. Prevalence and ethnic pattern of diabetes and prediabetes in China in 2013. *JAMA* 2017;317:2515–23.
4 Centers for Disease Control and Prevention. National diabetes statistics report 2020: estimates of diabetes and its burden in the united states. Available: https://www.cdc.gov/diabetes/data/statistics-report/index.html [Accessed 12 May 2022].
5 *IDF diabetes atlas*. 2021.
6 Xu Y, Wang L, He J, *et al*. Prevalence and control of diabetes in Chinese adults. *JAMA* 2013;310:948–59.
7 Fang M, Wang D, Coresh J, *et al*. Trends in diabetes treatment and control in U.S. adults, 1999-2018. *N Engl J Med* 2021;384:2219–28.
8 Doyle-Delgado K, Chamberlain JJ, Shubrook JH, *et al*. Pharmacologic approaches to glycemic treatment of type 2 diabetes: synopsis of the 2020 American diabetes association's standards of medical care in diabetes clinical guideline. *Ann Intern Med* 2020;173:813–21.
9 Turner RC, Cull CA, Frighi V, *et al*. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK prospective diabetes study (UKPDS) group. *JAMA* 1999;281:2005–12.
10 Chinese Diabetes Society. Guideline for the prevention and treatment of type 2 diabetes mellitus in china (2020 edition). *Chin J Diabetes Mellitus* 2021;13:315–409.
11 Chinese Diabetes Society, National Office for Primary Diabetes Care. National handbook for the prevention and control of diabetes in primary care (2019). *Chin J Intern Med* 2019:713–35.
12 FDA. Patient preference information - voluntary submission, review in premarket approval applications, humanitarian device exemption applications, and de novo requests, and inclusion in decision summaries and device labeling. 2016. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-preference-information-voluntary-submission-review-premarket-approval-applications
13 de Bekker-Grob EW, Ryan M, Gerard K. Discrete choice experiments in health economics: a review of the literature. *Health Econ* 2012;21:145–72.
14 von Arx L-B, Kjeer T. The patient perspective of diabetes care: a systematic review of stated preference research. *Patient* 2014;7:283–300.
15 Huang Y, Huang Q, Xu A, *et al*. Patient preferences for diabetes treatment among people with type 2 diabetes mellitus in china: a discrete choice experiment. *Front Public Health* 2021;9:782964.
16 Li Y, Teng D, Shi X, *et al*. Prevalence of diabetes recorded in mainland China using 2018 diagnostic criteria from the American diabetes association: national cross sectional study. *BMJ* 2020;369:m997.
17 Orme B. Sample size issues for conjoint analysis studies. In: *Sequim: Sawtooth Software Technical Paper*. 1998.
18 Draznin B, Aroda VR, Bakris G. 9. pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2022. *Diabetes Care* 2022;45(Suppl 1):S125–43.
19 Liu S, Liu J, Yu Y, *et al*. What is valued most by patients with type 2 diabetes mellitus when selecting second-line antihyperglycemic medications in china. *Front Pharmacol* 2021;12:802897.
20 Li C, Luo J, Jiang M, *et al*. The efficacy and safety of the combination therapy with GLP-1 receptor agonists and SGLT-2 inhibitors in type 2 diabetes mellitus: a systematic review and meta-analysis. *Front Pharmacol* 2022;13:838277.
21 Mearns ES, Sobieraj DM, White CM, *et al*. Comparative efficacy and safety of antidiabetic drug regimens added to metformin monotherapy in patients with type 2 diabetes: a network meta-analysis. *PLoS One* 2015;10:e0125879.
22 Tsapas A, Karagiannis T, Kakotrichi P, *et al*. Comparative efficacy of glucose-lowering medications on body weight and blood pressure in patients with type 2 diabetes: a systematic review and network meta-analysis. *Diabetes Obes Metab* 2021;23:2116–24.
23 Phung OJ, Scholle JM, Talwar M, *et al*. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic

control, weight gain, and hypoglycemia in type 2 diabetes. *JAMA* 2010;303:1410–8.
24 Nauck M, Frid A, Hermansen K, *et al*. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the lead (liraglutide effect and action in diabetes) -2 study. *Diabetes Care* 2009;32:84–90.
25 Bennett WL, Maruthur NM, Singh S, *et al*. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. *Ann Intern Med* 2011;154:602–13.
26 Du J, Liang L, Fang H, *et al*. Efficacy and safety of saxagliptin compared with acarbose in Chinese patients with type 2 diabetes mellitus uncontrolled on metformin monotherapy: results of a phase IV open-label randomized controlled study (the smart study). *Diabetes Obes Metab* 2017;19:1513–20.
27 Sun F, Chai S, Yu K, *et al*. Gastrointestinal adverse events of glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a systematic review and network meta-analysis. *Diabetes Technol Ther* 2015;17:35–42.
28 Bridges JFP, Hauber AB, Marshall D, *et al*. Conjoint analysis applications in health -- a checklist: a report of the ISPOR good research practices for conjoint analysis Task force. *Value Health* 2011;14:403–13.
29 Johnson FR, Hauber AB, P CM. *A brief introduction to the use of stated-choice methods to measure preferences for treatment benefits and risks (publication no.RR-0009-0909)*. Res Triangle Park: NC: RTI Press, 2009.
30 Hauber AB, González JM, Groothuis-Oudshoorn CGM, *et al*. Statistical methods for the analysis of discrete choice experiments: a report of the ISPOR conjoint analysis good research practices task force. *Value Health* 2016;19:300–15.
31 Pacifico D, Yoo H il. Lclogit: a stata command for fitting latent-class conditional logit models via the expectation-maximization algorithm. *The Stata Journal* 2013;13:625–39.
32 Yoo HI. Lclogit2: an enhanced module to estimate latent class conditional logit models. *SSRN Journal* 2019;13:1–20.
33 Purnell TS, Joy S, Little E, *et al*. Patient preferences for noninsulin diabetes medications: a systematic review. *Diabetes Care* 2014;37:2055–62.
34 Hauber AB, Tunceli K, Yang J-C, *et al*. A survey of patient preferences for oral antihyperglycemic therapy in patients with type 2 diabetes mellitus. *Diabetes Ther* 2015;6:75–84.
35 Donnan JR, Johnston K, Chibrikov E, *et al*. Capturing adult patient preferences toward benefits and risks of second-line antihyperglycemic medications used in type 2 diabetes: a discrete choice experiment. *Can J Diabetes* 2020;44:6–13.
36 Taylor SI. The high cost of diabetes drugs: disparate impact on the most vulnerable patients. *Diabetes Care* 2020;43:2330–2.
37 Patel MR, Piette JD, Resnicow K, *et al*. Social determinants of health, cost-related nonadherence, and cost-reducing behaviors among adults with diabetes: findings from the National health interview survey. *Med Care* 2016;54:796–803.
38 Hershey JA, Morone J, Lipman TH, *et al*. Social determinants of health, goals and outcomes in high-risk children with type 1 diabetes. *Can J Diabetes* 2021;45:444–50.
39 Toroski M, Kebriaeezadeh A, Esteghamati A, *et al*. Patient and physician preferences for type 2 diabetes medications: a systematic review. *J Diabetes Metab Disord* 2019;18:643–56.
40 NICE-SUGAR Study Investigators, Finfer S, Chittock DR, *et al*. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009;360:1283–97.
41 Davis S, Alonso MD. Hypoglycemia as a barrier to glycemic control. *J Diabetes Complications* 2004;18:60–8.
42 Mohamed AF, Zhang J, Johnson FR, *et al*. Avoidance of weight gain is important for oral type 2 diabetes treatments in sweden and germany: patient preferences. *Diabetes Metab* 2013;39:397–403.
43 American Diabetes Association. 8. obesity management for the treatment of type 2 diabetes: standards of medical care in diabetes-2020 *Diabetes Care* 2020;43(Suppl 1):S89–97.
44 Jianwei X, Fan Y. Budget impact analysis of benaglutide injection in the treatment of type 2 diabetes mellitus in chinese patients. *China Journal of Pharmaceutical Economics* 2021;14:5–12.
45 Kapitza C, Forst T, Coester HV, *et al*. Pharmacodynamic characteristics of lixisenatide once daily versus liraglutide once daily in patients with type 2 diabetes insufficiently controlled on metformin. *Diabetes Obes Metab* 2013;15:642–9.
46 Nauck M, Frid A, Hermansen K, *et al*. Long-Term efficacy and safety comparison of liraglutide, glimepiride and placebo, all in combination with metformin in type 2 diabetes: 2-year results from the LEAD-2 study. *Diabetes Obes Metab* 2013;15:204–12.
47 Mansfield C, Sikirica MV, Pugh A, *et al*. Patient preferences for attributes of type 2 diabetes mellitus medications in Germany and Spain: an online discrete-choice experiment survey. *Diabetes Ther* 2017;8:1365–78.
48 Casciano R, Malangone E, Ramachandran A, *et al*. A quantitative assessment of patient barriers to insulin. *Int J Clin Pract* 2011;65:408–14.
49 Shields BM, Angwin CD, Shepherd MH, *et al*. Patient preference for second- and third-line therapies in type 2 diabetes: a prespecified secondary endpoint of the trimaster study. *Nat Med* 2023;29:384–91.
50 Johnson FR, Ozdemir S, Mansfield C, *et al*. Are adult patients more tolerant of treatment risks than parents of juvenile patients? *Risk Anal* 2009;29:121–36.