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ORIGINAL ARTICLE

Patient preferences for treatment in type 2 diabetes: the Italian discrete-choice experiment analysis

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Abstract

Aims Several drug classes are now available to achieve a satisfactory metabolic control in patients with type 2 diabetes (T2DM), but patients' preferences may differ.

Methods In a discrete-choice experiment, we tested T2DM patients' preferences for recent antidiabetic drugs, in the event that their treatment might require intensification. The following attributes were considered: (a) route of administration; (b) type of delivery; (c) timing; (d) risk of adverse events; (e) effects on body weight. Twenty-two possible scenarios were built, transferred into 192 paired choices and proposed to 491 cases naïve to injectable treatments and 171 treated by GLP-1 receptor agonists (GLP-1RAs). Analyses were performed by descriptive statistics and random effects logit regression model.

Results Preferences according to dosing frequency, risk of nausea and urinary tract infections (UTIs) were similar across groups, age, sex and BMI. Administration route and delivery type accounted for 1/3 of relative importance; the risk of UTIs, nausea and dosing frequency for ≈ 20% each, and weight loss for only 6%. Two significant interactions emerged ($p < 0.01$): type of delivery × group, and weight change × BMI class. Irrespective of previous treatment, the three preferred choices were injectable, coupled with weekly dosing and a ready-to-use device (first two choices). In a regression model, being naïve or non-naïve changed the ranking of preferences ($p < 0.001$), and the order was systematically shifted towards injectable medications in non-naïve subjects.

Conclusion Easy-to-deliver, injectable treatment is preferred in T2DM, independently of treatment history, and previous experience with GLP-1RAs strengthens patients' willingness to accept injectable drugs.

Keywords Adverse events · Dose frequency · Glucagon-like peptide-1 receptor agonists · Injectable drugs · Nausea · Oral treatment · Route of delivery · Sodium–glucose co-transporter 2 inhibitors · Urogenital-tract infections · Weight loss

Introduction

Type 2 diabetes mellitus (T2DM) is a challenge for National Healthcare systems. The worldwide epidemics of obesity and the progressive increase in life expectancy are both contributing to raise the prevalence of disease in the community. The direct costs of the disease have increased as well [1], aggravated by the several comorbidities involving most organs and tissues, generally associated with poor metabolic control [2]. Intensive treatment with glucose-lowering drugs is mandatory at all stages of the disease, and new drug classes have recently been added to metformin and sulfonylureas in use since the early 1960s. Treatment results in poly-therapy, increasing the risk of reduced compliance and non-adherence.

Treatment targets and drug use are dictated by clinical practice guidelines, based on patients' frailty, safety and effectiveness of individual drug classes, and by the cost of treatment [3], with authorities regulating or monitoring the use of more expensive drugs in an attempt to control total expenditure in universalistic healthcare systems [4].

Patients' preferences are not adequately considered by diabetologists, more concerned with the need to prescribe

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according to guidelines, and rarely checking patients' preferences, intimately linked to adherence. A retrospective analysis in two large community-acquired UK databases found that 13–15% of patients might be classified as non-adherent (medical possession rate ≤ 80%) [5], and medication adherence ≥ 80% was demonstrated only in 6 out of the 27 studies analyzed in a systematic review [6]. Low adherence varies according to drug class [7], but uniformly impairs target reach and metabolic control [5, 8]. On the contrary, high adherence, although increasing drug spending, is reported to reduce hospitalization rate, thus saving total costs [9, 10]. In a very recent literature review, Kennedy-Martin et al. concluded that cost-savings generated from better adherence might be substantial, and the economic case prompts for the identification of strategies to facilitate drug adherence, coverage and persistence [7].

A critical issue in diabetes treatment is the passage from oral to injectable therapy. T2DM patients perceive the use of injectable drugs as a non-return step, marking a severe progression of the disease [11], associated with the use of insulin, blood glucose monitoring and complications. This is no longer the case after the marketing of glucagon-like peptide 1 receptor agonists (GLP-1RAs), which might be used at any stage of the disease [12]. A few data are available on clinical differences between patients initiating insulin vs. exenatide (the first non-insulin injectable treatment), including patient-reported outcomes [13–15]. However, fear of needle-associated pain, anxiety for poor ability to handle treatment, fear of complications and side effects, as well as perceived impact on quality of life have been reported also in 30–50% of patients at first GLP-1RA treatment proposal [16], and need adequate education.

The discrete-choice experiment (DCE) methodology is an accepted approach to evaluate patients' preferences in the presence of two or more possible treatment options. It offers patients the opportunity to provide grading of the perceived relative importance of treatment, including attributes related to route of administration, dosing frequency, potential risk of side effects, also impacting on health economics [17]. The methodology has been applied to detect patients' preferences for different GLP-1RAs, based on injection device, needle type, frequency of administration, refrigeration and injection-site reactions [18], as well as other attributes associated with different treatments (target reach, weight change, hypoglycemia and nausea) [19, 20]. However, limited analyses are available on patients' willingness to accept injectable treatments compared with add-on or new oral treatments, also considering possible side effects. These oral treatments (specifically, the class of sodium–glucose co-transporter 2 inhibitors—SGLT2-Is) might be a likely alternative for treatment intensification, but are associated with a significant risk of urogenital infections, to be balanced against the risk of nausea and gastrointestinal discomfort of GLP-1RAs [21].

The aim of the present analysis was to determine patients' preferences whenever treatment intensification or a new treatment strategy is needed to achieve a satisfactory metabolic control, both in subjects naïve to injectable glucose-lowering drugs and in those who have already experienced GLP-1RAs. The underlying hypothesis was that previous experience with injectable drugs, coupled with ready-to-use device and weekly dosing, might change the initial preference towards oral treatment, considering both the risk of adverse events and the easiness of injectable treatment.

Materials and methods

DCE design

Attributes for DCE analysis were selected on the basis of a review of attributes commonly included in studies of T2DM medications and according to the expert board (Table 1, top). The final number of attributes was five, consistent with other previously published DCE studies, including between three and seven attributes [22]. Unlike other DCE experiments in diabetes [19] where levels were defined taking into account the results of previous clinical trials, for this study the expert board chose dichotomous (yes–no) levels to facilitate patient selection.

The sample size was estimated considering the number of choice pairs (the expert board considered that eight choice pairs was a reasonable number) included in each DCE questionnaire, number of alternatives (two) per choice pair, and maximum number of levels (two) for attribute, with the exception of the attribute "Type of delivery" (three levels). For non-naïve patients, considering the more limited number of eligible T2DM cases, the number of paired choices per questionnaire was increased to twelve. Based on these study parameters as well as on the feasibility (recruitability), the number of participants was fixed at minimum 400 naïve and 150 non-naïve patients.

The choice sets were manually constructed: from the first $3 \times 2 \times 2 \times 2 \times 2 = 48$ possible combinations, a subset of 22 options was derived after the expert board excluded the unrealistic combinations (Table 1, bottom). Among the $22 \times 21/2 = 231$ possible pairwise comparisons, another subset was obtained after the elimination of trivial comparisons, reaching a final number of 192 comparisons, distributed in 24 different questionnaires, each comprising 8 choices (12 for non-naïve).

Notably, the different treatments proposed in paired choices were defined as equally effective in metabolic improvement and target reach, with different risks of possible adverse events.

Table 1 Attribute and levels for the discrete-choice experiment (top) and individual choices used in the program (bottom)

Attribute	Levels		
Type of delivery	Oral	Injectable Ready-to-use	Injectable To-be-prepared
Urogenital infections (UTI)	No risk	At risk	
Nausea	No risk	At risk	
Dose frequency	Weekly	Daily	
Weight	Diminished	Stable	

Option	Code	Frequency	Delivery	Weight	Nausea	UTI
1	A	Daily	Oral	Stable	No risk	At risk
2	B	Daily	Oral	Stable	At risk	No risk
3	C	Daily	Oral	Stable	At risk	At risk
4	D	Daily	Oral	Diminished	No risk	At risk
5	E	Daily	Oral	Diminished	At risk	No risk
6	F	Daily	Oral	Diminished	At risk	At risk
7	G	Daily	Ready-to-use	Stable	No risk	No risk
8	H	Daily	Ready-to-use	Stable	At risk	No risk
9	I	Daily	Ready-to-use	Diminished	No risk	No risk
10	J	Daily	Ready-to-use	Diminished	At risk	No risk
11	K	Daily	To-be-prepared	Stable	Low risk	No risk
12	L	Daily	To-be-prepared	Stable	At risk	No risk
13	M	Daily	To-be-prepared	Diminished	No risk	No risk
14	N	Daily	To-be-prepared	Diminished	At risk	No risk
15	O	Weekly	Ready-to-use	Stable	No risk	No risk
16	P	Weekly	Ready-to-use	Stable	At risk	No risk
17	Q	Weekly	Ready-to-use	Diminished	No risk	No risk
18	R	Weekly	Ready-to-use	Diminished	At risk	No risk
19	S	Weekly	To-be-prepared	Stable	No risk	No risk
20	T	Weekly	To-be-prepared	Stable	At risk	No risk
21	U	Weekly	To-be-prepared	Diminished	No risk	No risk
22	V	Weekly	To-be-prepared	Diminished	At risk	No risk

Participants

All consecutive subjects with T2DM attending the outpatient department of participating centers were asked to participate. The following eligibility criteria were considered: male or female > 18 years of age; diagnosed with T2DM; on oral medication for diabetes (excluding SGLT-2 inhibitors); willing and able to provide written informed consent. Participants were excluded if they had type 1 diabetes or gestational diabetes; T2DM treated only with diet and exercise. Eligible patients were divided into two groups: (a) never treated with injectable drugs for diabetes (naïve group); (b) previously treated with injectable medication for T2DM, including basal insulin and GLP-1RAs, but excluding basal-bolus therapy (non-naïve).

The metabolic control at time of DCE submission was not considered. During the outpatient visit and before clinical evaluation, the paired choices were proposed as part of a research study, aimed at detecting patients' preferences, without any relation with their present clinical status.

Study procedures

The study was conducted between July and October 2017 in nine diabetes centers, scattered throughout Italy (Northern Italy, three centers; Central Italy, 3three centers; Southern Italy, three centers). Surveys were administered in-person by trained facilitators, and patients self-completed the survey questions with their assistance (whenever needed).

Prior to completing the DCE questions, patients were asked to fill in a brief questionnaire on demographic and anthropometric characteristics, education level, job status, housing (family/caregivers), weight and height, time since diagnosis of diabetes, and type of treatment for diabetes (oral, injectable, oral + injectable). A brief description of the purpose of the study followed, i.e., to test patients' preferences considering the attributes of new drug classes available for diabetes treatment, each characterized by advantages and possible side effects. Accordingly, the participants were asked to select by pen-and-paper between pairs of hypothetical medications the ones they preferred. The participants reviewed the descriptions of attributes and levels before completing the paired DCE selection. In particular, they were explained that injectable drugs might be delivered either daily, via a multi-dose device, to be managed for correct delivery, or weekly, via a disposable device. In this latter case, however, two possibilities were available, either a ready-to-use device, or a device that had to be prepared before injection. Similarly, the participants were advised on the possible risk of adverse events following the use of new drug classes, namely either genito-urinary tract infections (UTIs) (approximately 5% of cases, more commonly in females) or nausea/gastrointestinal discomfort (on average, 10–20% of cases, but slowing down on repeated injections). The final attribute was the effect on weight of new antidiabetic drugs, considering that weight loss might considerably impact on patients' preferences. The amount of weight loss was quantified as less than 5% of body weight. No product names were mentioned anywhere in the program.

Following completion of the DCE survey, non-naïve participants were asked to answer two additional questions about adherence to diabetes treatment in general and following the start of injectable GLP-1RAs.

Statistical analysis

Descriptive statistics (frequencies, means and standard deviations) were reported for socio-demographic and clinical variables.

The DCE responses were analyzed using a random effects logit regression model.

To analyze the results of the DCE, part-worth utility estimates were computed for the overall sample, and by subgroups which resulted significantly associated with preference. Part-worth utility values provide information on the extent to which participants prefer each level of an attribute, and were scaled within each attribute to have a mean of 0. A positive value indicates that the attribute level is preferred, while negative values indicate a preference for other levels of the attribute. Larger part-worth utility values indicate a higher degree of preference. The part-worth utility values or preference weights reflect the strength of patients' preferences for each of the medication attributes. The RI of each attribute was calculated by summing up the range of part-worth utility values for all attributes (i.e., the largest minus the smallest part-worth utility values within each attribute), yielding the overall utility value, and by dividing the utility of each attribute by the overall utility value. The RI of each attribute (expressed as a percentage) thus reflects the proportion of the variance in the overall medication preference that is accounted for by each attribute.

Regression models with interaction effects were used to test for significant differences in preferences for the levels of each attribute across groups: naïve vs. non-naïve, age group (≤ 65 years vs. > 65 years), sex and BMI group (two classifications were considered, one with cut-point at 28 kg/m^2, corresponding to the median, thus producing 2 equal-size groups, and one with cut-point at 30 kg/m^2, corresponding to the conventional threshold of obesity).

Results

The two cohorts included in the study (naïve vs. non-naïve—Table 2) were very similar, with a marginally higher prevalence of males and higher educational status in non-naïve

Table 2 Socio-demographic and clinical characteristics of the population

	Naïve ($n=491$)	Non-naïve ($n=171$)	Statistical test (p value)
Sex, *n* (%)			
Female	220 (44.8%)	63 (36.8%)	Chi square = 3.287, $df=1$, $p=0.070$
Male	271 (55.2%)	108 (63.2%)	
Age (years)			
Mean (SD)	66.4 (9.3)	64.4 (9.9)	*t* test = 2.441, $df=660$, $p=0.015$
Marital status, *n* (%)			
Unmarried	39 (7.9%)	12 (7.0%)	Chi square = 3.287, $df=3$, $p=0.070$
Married	369 (75.2%)	126 (73.7%)	
Divorced	28 (5.7%)	15 (8.8%)	
Widowed	55 (11.2%)	18 (10.5%)	
Education, *n* (%)			
Primary	158 (32.2%)	39 (22.8%)	Chi square = 8.860, $df=3$, $p=0.065$
Secondary	155 (31.6%)	56 (32.7%)	
High school	136 (27.7%)	53 (31.0%)	
College	42 (8.6%)	23 (13.5%)	
Living with, *n* (%)			
Family	212 (43.2%)	70 (40.9%)	Chi square = 2.893, $df=5$, $p=0.716$
Partner	174 (35.4%)	64 (37.4%)	
Sons	21 (4.3%)	10 (5.8%)	
Parents	9 (1.8%)	1 (0.6%)	
Alone	70 (14.3%)	23 (13.5%)	
Paid caregiver	5 (1.0%)	3 (1.8%)	
Diabetes duration, *n* (%)			
< 1 year	51 (10.4%)	10 (5.9%)	Chi square = 5.149, $df=3$, $p=0.272$
1–5 years	107 (21.8%)	39 (22.8%)	
6–10 years	124 (25.3%)	46 (26.9%)	
> 10 years	209 (42.6%)	76 (44.4%)	
BMI (kg/m^2)			
Mean (SD)	29.3 (5.6)	29.7 (5.1)	*t* test = 2.441, $df=660$, $p=0.432$

cases. Non-naïve patients were slightly younger ($p=0.015$), even if the absolute difference was very small (2.1 years) and the standardized difference can be considered small (mean difference/SD = 0.21). BMI was similar, with approx. 50% of both males and females in the obesity range, independently of injectable treatment history.

DCE results

According to random effect logit regression model, in the total sample every attribute had a significant effect on patients' choice. Their part-worth utility and relative importance are reported in Table 3. As to the relative importance (RI), in the whole group the type of delivery remained the most important attribute accounting for over one-third of patients' preferences (34%). The risk of UTIs (22%), nausea (20%) and dose frequency (19%) followed, and a very small fraction was left to weight change (6%). Notably, the RI was different when split according to previous experience. Whereas in naïve patients the RI assigned to route and device of administration was as high as 40%—and the oral route was preferred—in non-naïve cases the RI of this attribute decreased to only 24%—a value similar to the risks of main adverse events—and injection was now the preferred route. In this last cohort, with higher BMI, the RI of the effects on body weight increased to 10% (Fig. 1).

While preferences expressed in relation to dosing frequency, risk of nausea and risk of UTIs were substantially similar across groups (naïve vs. non-naïve), age (> 65 vs. ≤ 65), sex (M vs. F) and BMI (> 28 kg/m^2 vs. ≤ 28), two interactions emerged as highly significant ($p<0.01$): type of delivery × group and weight change × BMI class, i.e., the type of delivery was remarkably different according to previous experience with injectable GLP-1RAs, whereas a weight change was only significant in the presence of obesity (Fig. 2; Supplemental Table 1). Similar findings were observed when the cut-off for BMI was set at 30 kg/m^2.

Patients' preferences were significantly modulated by the combination of different attributes, ranging from above 80% for the most preferred ones to only about 15% for the least

Table 3 Part-worth utilities, relative importance and ranking of attributes in the overall sample

Attribute	Attribute levels	Part-worth utility (SE)	Relative Importance	Rank
Type of delivery	Oral	0.173 (0.009)	0.34	1
	Ready-to-use	−0.027 (0.009)		
	To-be-prepared	−0.147 (0.008)		
Urogenital infections	No risk	0.110 (0.003)	0.22	2
	At risk	−0.110 (0.011)		
Nausea	No risk	0.100 (0.005)	0.20	3
	At risk	−0.100 (0.007)		
Dose frequency	Weekly	0.095 (0.008)	0.19	4
	Daily	−0.095 (0.005)		
Weight	Diminished	0.030 (0.006)	0.06	5
	Stable	−0.030 (0.006)		

Part-worth utility values provide information on the extent to which participants prefer each level of an attribute and are scaled within each attribute to have a mean of 0 (*SE* standard error). A positive part-worth utility value indicates that the attribute level is preferred. The overall utility values represent the range of utility values within each attribute. Relative importance is calculated as: overall utility for each attribute/total utility values.

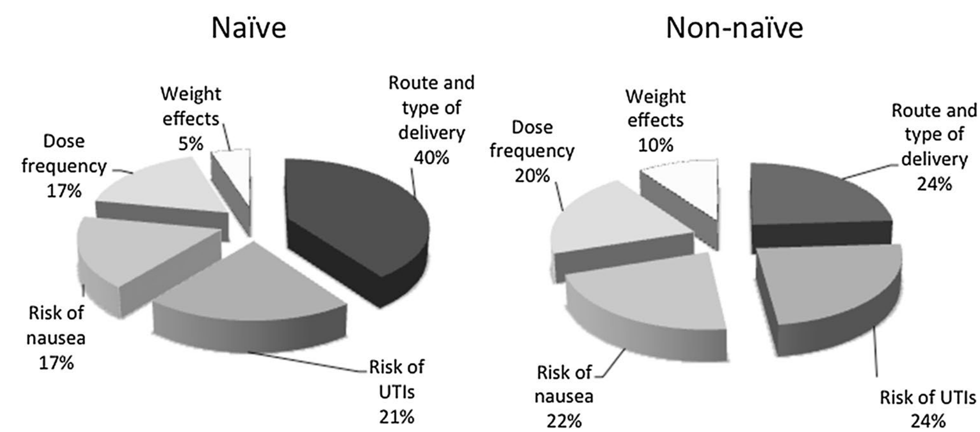

Fig. 1 Relative importance of different attributes in naïve and non-naïve patients

(Fig. 3). However, being naïve or non-naïve significantly affected the ranking of preferences, as indicated by medications × group interaction (Wald Chi-square = 87.0; $df = 22$; $p < 0.001$). The first three preferred hypothetical medications (Fig. 3, top, in the order column Q, O, and U) were the same in both groups of patients, i.e., willingness to accept injectable treatment was high when the hypothetical treatment was coupled with the attributes of weekly dosing and ready-to-use device (Fig. 3, top, column O–R). The order of preferences remarkably differed for other choices: with the above exceptions, oral medications (A–F) were given higher scores by patients naïve to injections compared with non-naïve, whereas non-naïve patients frequently scored higher the injectable hypothetical medications. In particular, large differences between naïve and non-naïve occurred for E, B, D oral medications (ranked fourth, fifth and sixth in naïve) for which the preferences were 15%, 25% and 17% lower in non-naïve, respectively.

Treatment adherence

Non-naïve patients self-reported complete adherence to previous oral glucose-lowering treatment only in 36% of cases; in 14% of cases, treatment was missed more than once a month, in 18% approximately once a month, in 13% once every 3 months, in 18% more rarely. Fifty-seven percent of interviewed patients reported that the use of injectable treatment had favored their adherence to the planned therapeutic regimen.

Discussion

The study provides evidence for a general preference of simplified injectable treatment with glucose-lowering drugs in patients with T2DM, questioning the common belief that the oral route of treatment administration is always preferred.

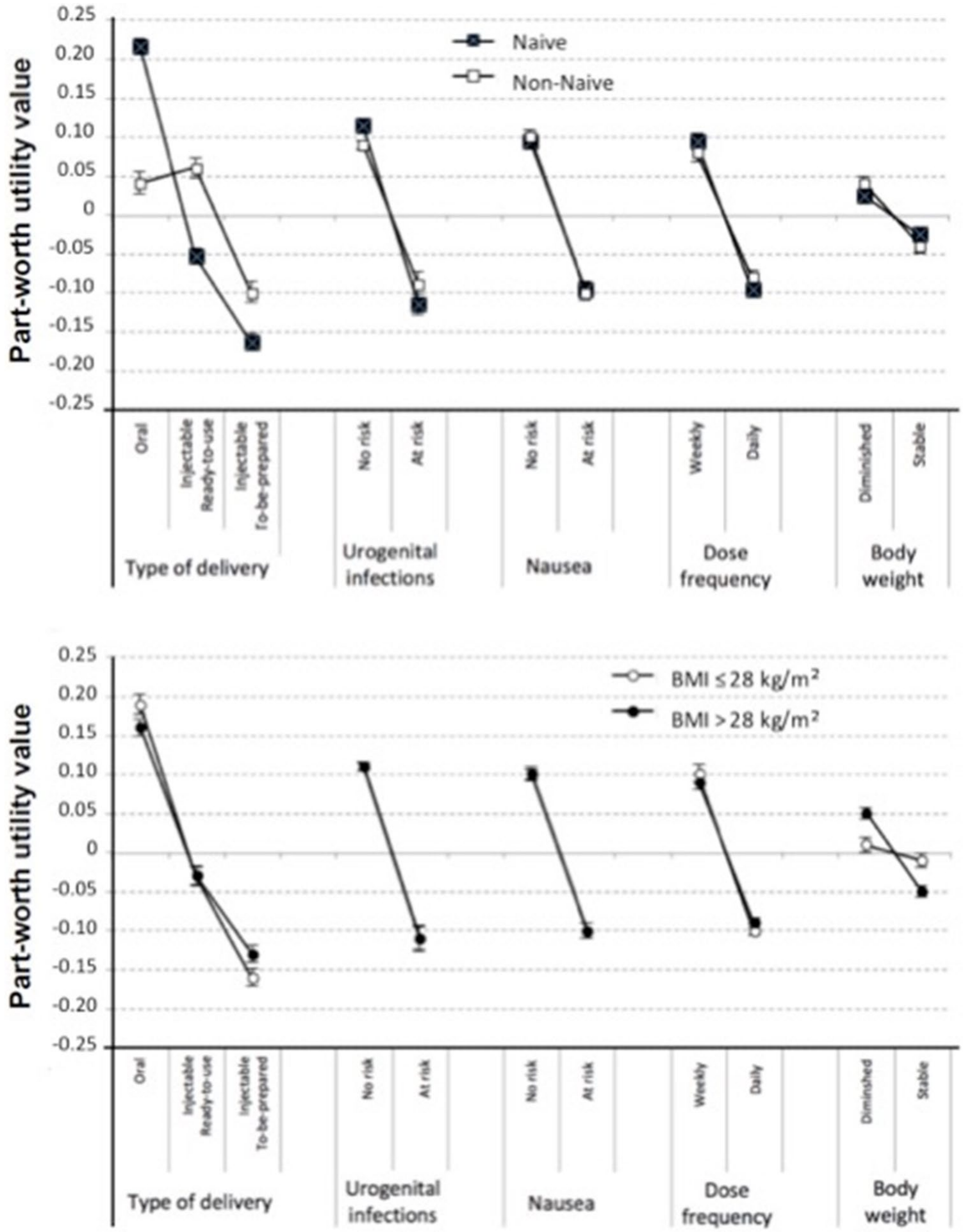

Fig. 2 Patients' preferences according to previous injectable treatment status (top) and BMI (bottom). Note that preferences in relation to urogenital infections, nausea and dose frequency are not modulated by patients' characteristics

In the event of an insufficient metabolic control, the most acceptable strategies were those based on the use of injectable drugs, provided they were not burdened by adverse events. In general, any new treatment carries a specific risk of adverse events; in naïve patients the route and method of administration was given the highest score in importance, but in non-naïve cases the route of delivery was scored much less, and not much more than the risk of adverse events (both UTIs and gastrointestinal symptoms). Notably, in this last subgroup, the administration via a disposable, ready-to-use, easy device was the attribute preferred to the oral route, particularly when coupled with weekly administration.

This is the largest study ever planned on patients' preferences in Italy, specifically addressing the most recent drugs available for treatment intensification. Contrary to several studies testing individual injectable drugs and focusing on very specific attributes (e.g., needle length, needle handling, device size, titration) [19, 23–26], the availability of the new SGLT2-Is raised the pivotal question of patients' preferences towards oral vs. injectable drugs in treatment intensification, with totally different risks of adverse events. DCE studies may be planned to answer two different questions, i.e., either testing attributes related to the overall process of care and providing clues to general patients' preferences, or testing specific attributes that inform on decisions related to very selected, specific contexts. To facilitate patients' selection, we only included broad, easy-to-identify attributes in our analysis, not quantitative attributes.

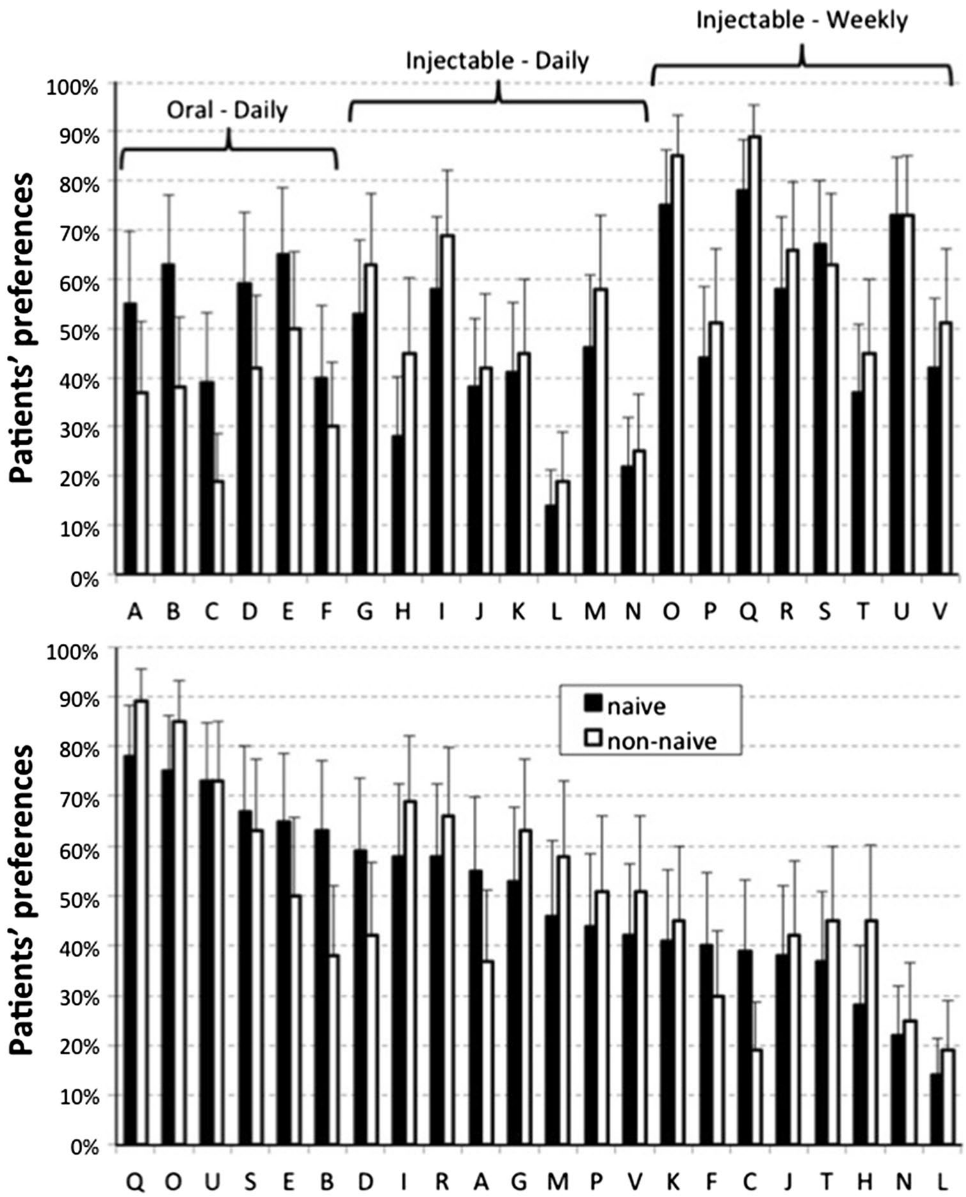

Fig. 3 Preferences to individual treatment in injectable treatment-naïve (closed columns) and non-naïve (open columns) T2DM patients. Columns are ranked in alphabetical order (top), with oral medications corresponding to letter A–F, daily injections to G–N (ready-to-use device, G–J; to-be-prepared device, K–N) and weekly injections to O–V (ready-to-use device, O–R; to-be-prepared device, S–V), and according to preferences in naïve patients (bottom). For definition of other attributes, see Table 1. Note that the three most preferred combinations of attributes in both naïve and non-naïve patients are weekly injections, with ready-to-use device, no risk of nausea or UTIs and diminished (Q) or stable body weight (O) or with to-be-prepared device, no risk of nausea and UTIs and diminished body weight (U)

In previous DCE analyses, the possibility to reach specific HbA1c or weight loss targets, or the severity of side effects, were defined by quantitative, multiple cut-offs [27]. This policy multiplies the number of paired choices, thus requiring a very large population, and would be mandatory for the definition of metabolic targets. According to the most recent guidelines, the definition of optimum metabolic control has indeed moved from a well-defined HbA1c value to targets tailored on age, frailty and comorbidities [28]. Patients may find it difficult to appreciate all advantages of more challenging targets, as well as the risks associated with stricter control, and the proper selection is left to the physicians who have all the information needed. HbA1c levels were not registered in our patients, and at time of paired choices—frequently proposed in the waiting room—several cases might be unaware of the last biochemistry. Further studies are thus needed to address the possible effect of metabolic control on patients' preferences, in the hypothesis that individuals with higher HbA1c values may be more open minded to injections. We preferred a less precise definition of risks and targets, just explaining only the possible problems and benefits in a pre-test information sheet, also including an exhaustive definition of the concept of risk and average figures of the estimated risks. To remove barriers to injection, in other DCE studies the presentation of injectable drugs was accompanied by videos, showing the easiness of injection and expected to increase willingness to accept GLP-1RA treatment [19].

The first attribute was "route and way of delivery". Whereas the difference between oral and injectable route is self-evident, for naïve patients the difference between a device needing appropriate drug-dose selection (multi-dose pen) and/or drug suspension before injection was explained in detail. This attribute had previously been tested in a specific comparison between liraglutide and dulaglutide, with results largely in favor of the single-use pen [19]. In a comparison between liraglutide and once-weekly exenatide the need for titration and preparation before injection were tested as separate attributes, and patients enrolled in several European countries preferred a multi-use pen over a vial/syringe [23, 24]. However, technological improvements have remarkably changed the devices of GLP-1RA delivery, and some attributes are obsolete. A literary review identified 31 attributes tested in DCE studies carried out in patients with diabetes—and 61 more in non-DCE studies [29]; among device-related attributes, injection preparation was considered one of the most important factors dictating patients' preferences.

Safety concerns were included in the analysis, and both the risk UTIs and or nausea/gastrointestinal discomfort were included as attributes. The relative importance given to these adverse events was very similar, with a marginally higher importance for UTIs, perceived as a relevant attribute both in naïve and non-naïve cases. To this purpose, cases treated with SGLT2-Is were excluded from the analysis, since this type of adverse event had already been discussed at time of add-on SGLT2-I treatment. The prevalence of adverse events is variable in the population, leading to treatment withdrawal in a proportion of cases treated by GLP-1RAs, because of nausea [30], and because of UTIs in subjects treated with SGLT2-Is. The prevalence of these risks in treated patients was explained to patients, and was given approximately the same relative importance by patients, although the severity of SGL2-I-associated UTIs may be more threatening. Anyway, attributing to nausea approximately the same relative importance given to the highly appreciated change from daily to weekly injection is confirmative of the attention to safety concerns and to immediate consequences of medications, already reported in a DCE analysis [31].

Finally, we included weight loss as an important attribute, considering that most patients with T2DM are continuously and unsuccessfully striving to lose weight, as recommended by physicians. In keeping with previous results, this attribute was mainly considered in subjects with obesity. In the setting of non-naïve cases, the much higher relative importance given to weight loss may stem from both the higher BMI and the personal experience of weight loss following GLP-1RA treatment. Gelhorn et al. reported a higher relative importance of weight loss attributed by women [19], consistent with the much higher body image dissatisfaction in women with obesity, at similar BMI [32].

We did not include the risk of hypoglycemia among possible attributes, despite the large impact on daily life of any hypoglycemic event. The impending risk of hypoglycemia scored very high among patients on insulin treatment in previous DCE analyses, driving preferences in both type 1 and type 2 diabetes [27, 33]. However, all new glucose-lowering drug classes are characterized per se by a very low risk of hypoglycemia, and not appreciably different between SGLT2-Is, GLP-1RAs and also DPP4-Is, and should no longer be included in DCE analyses in T2DM.

Contrary to DCE performed in other settings [34, 35], also cost was not considered in the analysis. Cost was the most important attribute in countries where private insurance methods are operative, not only the United States [34], but also in Germany [35], and the yearly cost between different anti-hyperglycemic drug classes, varying by a factor of 20 in Italy, may make the difference. The universalistic, Beveridge type, Italian health system completely covers drugs for diabetes, and cost is scarcely considered by patients with diabetes, used to having any drug for free.

The cost of diabetes and its complications is continuously growing in Italy [2], and it is putting the National Health System at risk. However, the cost of drugs covers a minor part of total costs of diabetes, the highest proportion being the cost of non-glucose-lowering drugs and of hospital admittance [36]. Patients with diabetes commonly receive multiple treatments, in addition to glucose-lowering drugs. One or more antihypertensive drug classes, statins, beta-blockers, anti-platelets frequently sum up to more than ten pills/day, and any new oral treatment increases the risk of lower and lower adherence [37]. Moving to injectable treatment—and weekly treatment is an additional plus—may help increase adherence and compliance, as also suggested by non-naïve patients who completed the additional questionnaire. In this limited analysis, the results were not defined according to daily or weekly GLP-1RA administration. In a similar enquiry on the possible role of weekly vs. daily injectable GLP-1RAs conducted in naïve patients, twice as many patients answered that a weekly administration was expected to be much easier to follow, with a lower rate of missing injections [24]. Future studies are needed to demonstrate how much compliance and adherence may be increased by injectable, weekly GLP-1RA treatment in the real world, which also offers the possibility of anticipating or delaying injections by 1–2 days, and how much this translates into stricter metabolic control. In another setting with patients subjects to multiple complex therapies—and T2DM patients have to adhere to multiple therapies—it was demonstrated that a program to increase awareness of risks and benefits of treatment increased adherence by 15% in subjects receiving prescriptions according to preferences vs. a mere 6% in subjects prescribed a preference-discordant strategy [38].

In summary, this DCE analysis provides important clues to plan intensification treatment in subjects with T2DM. To get the best results from the many available options, patients' preferences should be carefully considered by physicians [39]. DCE studies have been important to cast doubts on the common belief that oral treatment is always the favorite solution. In general, the specific context of individual patients, their clinical characteristics, their beliefs, as well as the very many features dictating adherence and compliance, should receive a larger attention to keep patients at prespecified, desirable and tailored metabolic targets and reduce morbidity [40], disease progression and eventually mortality.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Research involving human and/or animal rights All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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