Exploring Patient Preferences for Adjunct-to-Insulin Therapy in Type 1 Diabetes

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OBJECTIVE

While sodium–glucose cotransporter inhibitor (SGLTi) therapy has been evaluated in type 1 diabetes (T1D) trials, patient reactions to benefits and risks are unknown. Using established methodology, we evaluated patient preferences for different adjunct-to-insulin therapy options in T1D.

RESEARCH DESIGN AND METHODS

An online survey, completed by 701 respondents with T1D (231 U.S., 242 Canada, and 228 Germany), used conjoint analysis to present six hypothetical, masked, pairwise drug profile choices composed of different benefit-risk attributes and effect ranges. Data used in analyses were derived from actual phase 3 trials of a low-dose SGLTi (comparable to oral empagliflozin 2.5 mg q.d.), a high-dose SGLTi (comparable to oral sotagliflozin 400 mg q.d.), and an available adjunct-to-insulin therapy (comparable to subcutaneous pramlintide 60 μg t.i.d.).

RESULTS

Conjoint analysis identified diabetic ketoacidosis risk as most important to patients (23% relative score; *z* test, $P < 0.05$); ranked second were HbA_{1c} reduction (14%), risk of severe hypoglycemia (13%), oral versus injectable treatment (12%), and risk of genital infection (12%). Next was risk of nausea (11%), followed by weight reduction (8%) and the risk of diarrhea (7%). A low-dose SGLTi drug profile was identified by conjoint analysis as the top patient preference (83% of participants; *z* test, $P < 0.05$) versus high-dose SGLTi (8%) or pramlintide (9%). Separate from conjoint analysis, when respondents were asked to choose their preferred adjunct-to-insulin therapy (masked to drug name/dose), 69%, 17%, 6%, and 9% of respondents chose low-dose SGLTi, high-dose SGLTi, pramlintide, and insulin therapy alone, respectively.

CONCLUSIONS

Low-dose SGLTi profile was the favored adjunct-to-insulin therapy by persons with T1D.

Recent diabetes management guidelines for the treatment of type 2 diabetes (T2D) from the American Diabetes Association and the European Association for the Study of Diabetes call for a patient-centric approach to enhance patient engagement in treatment decisions (1). Similar approaches are also important for persons with type 1 diabetes (T1D). It is therefore crucial to objectively evaluate patient preferences on attributes of new antidiabetes agents using well-established methodologies.

Patients living with T1D have relied, for nearly a century, solely on exogenous insulin administration as the mainstay of therapy for survival with no other reliable treatment

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options available to date. While advances in insulin delivery, continuous glucose monitoring (CGM), and improvement in insulin formulations have facilitated achieving glucose control, management remains complex and most patients are inadequately controlled (2,3). Adjunctive therapies to insulin in T1D are critically needed, but, as of 2018, only pramlintide has been approved in the U.S. Pramlintide's efficacy profile in T1D, evidenced by a placebo-corrected HbA_{1c} reduction in the range of 0.25–0.33% (2.7–3.6 mmol/mol), is offset by a twofold increase in the risk of severe hypoglycemia and the need for multiple daily injections, thereby limiting its clinical use (4,5).

In recent years, several molecules in the sodium–glucose cotransporter inhibitor (SGLTi) class including empagliflozin, dapagliflozin, and sotagliflozin have been studied in T1D in large phase 3 clinical trials (6–12). The positive benefit-risk profile of some of these agents, such as empagliflozin and dapagliflozin, has already been established in T2D, where these agents are indicated to improve glycemic control. Empagliflozin, specifically, has also been shown to reduce the risk of cardiovascular death in patients with T2D and established cardiovascular disease, and both empagliflozin and dapagliflozin appear to reduce hospitalization for heart failure and improve renal outcomes in T2D (13–15).

Overall, SGLTi studies in T1D have shown a dose-dependent improvement of efficacy outcomes including benefits on HbA_{1c} (-0.25% to -0.5% [-2.7 to -5.5 mmol/mol]), body weight (-2 to -3 kg), systolic blood pressure (-2 to -4 mmHg), and CGM-based glucose time in range (adding 1–3 h/day) (6–12). The efficacy observed with the SGLTi class in T1D has, however, come at an expense of an increased risk of genital infection (approximately a threefold increase vs. placebo) and, most importantly, an increased risk of diabetic ketoacidosis (DKA) of approximately three- to eightfold versus placebo for higher studied dose strengths (6–8). Interestingly, based on the empagliflozin T1D clinical development program, the lower empagliflozin 2.5 mg dose has not shown an increased risk for DKA versus placebo (8).

Indeed, concerns have been raised regarding the observed increased risk of DKA with the use of SGLTi in T1D despite risk mitigation strategies used in clinical trials (16,17). In this regard, post hoc analyses are being carried out to identify optimal T1D patient profiles for safe use of these agents. For example, the recent dapagliflozin and sotagliflozin approval by European regulators as adjunct to insulin therapy in T1D has been restricted in those with a BMI of ≥ 27 kg/m^2. Some clinical experts have also advocated for the potential use of the lowest available dose strength of an SGLTi as another DKA risk mitigation strategy in T1D (18). However, little is known from objective analyses about the patient perspectives and preferences related to the overall SGLTi benefit-risk value proposition in T1D, including key efficacy and safety outcomes.

Given that patient voice is of central importance in therapeutic decision-making, we performed a survey-based study using a "discrete choice experiment" form of conjoint analysis, a validated and well-established methodology (19). Conjoint analysis was used to objectively evaluate the preferences of patients with T1D for adjunct-to-insulin therapy options including a low-dose SGLTi (comparable to oral empagliflozin 2.5 mg q.d.), a high-dose SGLTi (comparable to oral sotagliflozin 400 mg q.d.), and currently available adjunct-to-insulin therapy (subcutaneous pramlintide 60 μg t.i.d., approved for use in T1D in the U.S.).

RESEARCH DESIGN AND METHODS

Respondent Recruitment and Inclusion Criteria

Inclusion criteria for this survey required respondents to be adults diagnosed with T1D and residing in the U.S., Canada, or Germany. Respondents were recruited from dQ&A's (San Francisco, CA) panel of patients with T1D engaged in a Web-based community. In Canada and Germany, additional respondents with HbA_{1c} >8.0% (>64 mmol/mol) were screened and recruited from a general Web-based consumer panel to reflect the average standard of care currently achieved in terms of glycemic control in routine clinical care (e.g., similar to the T1D Exchange Registry) (2,3). Based on the nature of this survey, including the use of anonymous responses, there was no requirement for the involvement of an ethics board. Respondents received a nominal payment (U.S., US$10; Canada, Can$15; Germany, €12) for their dedicated time to complete the survey, which took a median of 15 min to complete.

Conjoint Analysis and Selection of Attributes/Levels

A "discrete choice experiment" form of conjoint analysis was used in this study to determine the preferences that patients with T1D implicitly place on specific treatment efficacy and safety attributes of adjunct-to-insulin therapy options. The list of selected attributes included treatment delivery (oral tablet vs. injectable), HbA_{1c} reduction, weight reduction, risk of DKA, risk of severe hypoglycemia, risk of diarrhea, risk of nausea, and risk of genital infection. Various levels for each attribute were also defined, including options such as medication treatment form, various treatment effect sizes, or different safety risks for each attribute as applicable. The attributes and levels presented to the patient participants are summarized in Table 1.

Product attributes and levels were determined according to the published characteristics of drug profiles for oral empagliflozin 2.5 mg q.d., oral sotagliflozin 400 mg q.d., and the subcutaneous injection of pramlintide 60 μg t.i.d. The profile for the various drug options and levels of various attributes were adapted based on the safety and efficacy demonstrated in the placebo-controlled phase 3 clinical trial data for empagliflozin, sotagliflozin, and pramlintide evaluated as adjunct-to-insulin in T1D (4,7,8).

The research qualified the relative importance of the benefits and risks overall and among predefined subgroups of respondents. Expected respondent preference outcomes (also referred to elsewhere in the literature as "preference shares"), defined as the composite of attributes based on the medication efficacy and safety profiles from empagliflozin 2.5 mg q.d., sotagliflozin 400 mg q.d., and pramlintide 60 μg t.i.d., were also calculated.

Explicit Choice Assessments

The conjoint analysis was also complemented by an explicit choice questionnaire composed of the following: *1*) A separate question in which respondents were asked to explicitly choose, masked to drug name and dose, from a drug profile comparable to a low-dose oral

Table 1—Attributes and levels used in conjoint analysis

Attributes	Levels
Treatment form	A pill once a day Injections three times a day
HbA_{1c} reduction	0.23% (2.5 mmol/mol) 0.28% (3.1 mmol/mol) 0.46% (5.0 mmol/mol)
Weight reduction	4.0 lbs (1.8 kg) 4.4 lbs (2 kg) 6.5 lbs (3 kg)
Risk of DKA	No change 5 times increase
Risk of severe hypoglycemia	No change 2 times increase
Risk of diarrhea	No change 2 times increase
Risk of nausea	No change 4 times increase
Risk of genital infection	No change 2 times increase 3 times increase

SGLTi referred to as "Medication X," a high-dose oral SGLTi referred to as "Medication Y," or an available injectable therapy referred to as "Medication Z" as an adjunct therapy in T1D (Table 2). In addition, a "none of the above" response option was also available to respondents should they have opted not to choose any of the three proposed medication profiles (X, Y, or Z). At the time of the design and conduct of this scientific survey, no SGLTi had gained regulatory approval for use in T1D. The survey was fielded from 3 October to 29 October 2018. *2*) The likelihood of taking each of the three predefined choices (Medication X, Medication Y, and Medication Z as an adjunct to ongoing insulin therapy) was also characterized. The likelihood-to-adopt assessment was quantified based on a 4-point scale (definitely not/unlikely/likely/definitely) in addition to the estimation of a weighted likelihood score defined as 50% weight for the "definitely" responses plus a 25% weight for the "likely" responses.

Data Handling

In accordance with best practice, all incomplete responses, defined as surveys started by respondents but not fully completed and surveys completed in an unrealistically short time (defined as <7 min based on the minimum amount of time required to read and answer all questions) were removed to produce a final validated data set (overall, 122 [15%] of surveys were excluded). The identifiable details related to drug profiles and the sponsor were masked in the online survey, such that participants were not made aware of the sponsor, name of drug profiles used to derive attributes and levels, or dosage strengths. The sponsor had no access to the identities of the participants. No product, company, or brand names were mentioned in the survey.

Prior to the start of the survey, in a preamble section, respondents were objectively presented with descriptions of various drug benefits and risks, including the way benefit/risk outcomes and data were interpreted and summarized in the context of a placebo-controlled study. The incidence rates for identified risk attributes in the control group were based on completed phase 3 placebo-controlled clinical trials of empagliflozin, sotagliflozin, and pramlintide. Respondents were made aware of the incidence rates of various risk factors during placebo treatment as observed in clinical trials (4,7,8). Patients were also briefed and thereafter tested in the preamble section of the survey about the meaning of a placebo-controlled trial and the interpretation of incidence rates and incidence rate ratios (relative risks).

For the conjoint analysis section of this survey, respondents were presented with six pairwise choices between "packages" of eight attributes (i.e., medication benefits and side effects/risks). Their answers were used to calculate the importance of one attribute relative to another for the entire population and

Table 2—Masked drug profiles used in explicit choice analyses

	Medication X (comparable to empagliflozin 2.5 mg q.d.)	Medication Y (comparable to sotagliflozin 400 mg q.d.)	Medication Z (comparable to pramlintide 60 μg t.i.d.)
Treatment form	A pill once a day	A pill once a day	Injections three times a day
HbA_{1c} reduction	0.28% (3.1 mmol/mol)	0.46% (5.0 mmol/mol)	0.23% (2.5 mmol/mol)
Weight reduction	4 lbs (1.8 kg)	6.5 lbs (3 kg)	4.4 lbs (2 kg)
Risk of DKA	No change	5 times increase	No change
Risk of severe hypoglycemia	No change	No change	2 times increase
Risk of diarrhea	No change	2 times increase	No change
Risk of nausea	No change	No change	4 times increase
Risk of genital infection	2 times increase	3 times increase	No change

for different segments of the respondent pool. These data were also used to objectively estimate patient drug profile preference outcomes in the overall respondent pool and subgroups.

In addition, in the explicit choice section of the survey, direct respondent preferences, with respondents having full knowledge of the three drug profiles, were calculated, and the respondent likelihood to take the various drug options was also quantified.

The results from the conjoint analysis and the explicit choice questions were also analyzed according to the following subgroups (% of total): country (U.S. [33%], Canada [35%], and Germany [33%]), HbA_{1c} of >7.5% to ≤8% (>58 to ≤64 mmol/mol) (33%) or >8% (>64 mmol/mol) (67%), age (18–29 years [16%], 30–44 years [43%], 45–64 years [34%], and ≥65 years [7%]), BMI (<25 kg/m^2 [38%], 25 to <30 kg/m^2 [32%], and ≥30 kg/m^2 [27%]), DKA history (within the last 3 years [24%] and within the last 1 year [9%]), severe hypoglycemia history (within the last 3 years [51%] and within the last 1 year [30%]), CGM (52%) versus no CGM (48%), pump (65%) versus MDI (35%), and female (58%) versus male (42%).

Statistical Analysis

Statistical significance for all analyses was tested at the 90% confidence level using a two-tailed *z* test. Differences between importance scores in the conjoint analysis were tested for statistical significance at the 90% confidence level to produce a ranking of importance by the scores (summed to 100%). Attribute importance scores and other results were rounded to whole numbers. Based on a pairwise statistical testing strategy, attributes that were not statistically different from one another were assigned the same rank. Scores were tested in descending order against the highest numerical score. All scores statistically similar to a higher score were "promoted" to the higher rank until a statistically significant difference was found.

RESULTS

Baseline Clinical Characteristics

Valid complete surveys from 701 respondents were received (out of 1,078 dispatched) and analyzed, with 231 (33%) completed in the U.S., 242 (35%) in Canada, and 228 (33%) in Germany (Fig. 1*A*). Of these, 228 patients (33%) had HbA_{1c} of >7.5% to 8.0% (>58 to 64 mmol/mol) and 473 patients (67%) had HbA_{1c} >8.0% (>64 mmol/mol). Mean ± SD HbA_{1c} for the respondent population was 8.5% ± 0.68% (69 ± 7.4 mmol/mol) and mean duration of diabetes was 23.1 ± 13.3 years.

Conjoint Analysis Findings

Importance of Attributes

The conjoint analysis weighed (out of 100%) the various attributes by their relative importance (Fig. 1*B*). Based on the overall responder analysis, the risk of DKA was identified as the most important attribute to patients with a relative weighted score of 23% (*z* test, $P < 0.05$). This was followed by similarly ranked HbA_{1c} reduction (14%), risk of severe hypoglycemia (13%), oral versus injection treatment (12%), and risk of genital infection (12%). Risk of nausea was ranked next (11%), followed by weight reduction (8%) and risk of diarrhea (7%), which were ranked least important (Fig. 1*B*). Subgroup analyses did not show statistically significant differences regarding attribute importance and ranking compared with the rankings obtained in the overall population (data not shown).

Respondent Preference Outcomes

As part of the conjoint analysis and based on the set of attributes used in the analysis, drug profiles comparable to a low-dose oral SGLTi had a significantly higher preference outcome in the overall population relative to the high-dose oral SGLTi profile or the currently available injectable adjunctive therapy profile (see Fig. 1*C*). The low-dose SGLTi profile garnered 83% of the total preference outcomes for all respondents (*z* test, $P < 0.05$) compared with 8% for a high-dose SGLTi option and 9% for the current therapy option (Fig. 1*B*). Notably, the preference outcome for a low-dose SGLTi option was 95%, 82%, and 74% in the U.S., Germany, and Canada, respectively.

Head-to-head Explicit Medication Profile Comparison

When respondents were asked directly which of the medication profiles (masked to drug name and dose) they would select if they were to start on a medication in addition to their insulin regimen, 69% selected a low-dose oral SGLTi drug profile, 17% selected the high-dose oral SGLTi option, and 6% selected the current injectable adjunctive therapy option, while 9% opted to not take any of the three choices (*z* test, $P < 0.05$) (see Fig. 2*A*).

Estimates of the Likelihood to Adopt Each Medication Profile

When asked about their likelihood to take each medication, respondents were significantly more likely to say they would "definitely" or "likely" take a low-dose SGLTi (35% and 52%, respectively) compared with high-dose SGLTi (7% and 39%, respectively) or currently available T1D adjunctive injection therapy (5% and 40%, respectively) (see Fig. 2*B*). The adjusted likelihood score (a weighted score represented as 50% of the "definitely" score plus 25% of the "likely" score) was also significantly higher for a low-dose oral SGLTi at 31% vs. 13% for a high-dose oral SGLTi and 12% for currently available adjunctive injectable therapy ($P < 0.05$).

CONCLUSIONS

To our knowledge, this survey with a validated methodology is the first to highlight the relative importance that persons living with T1D place on the various risk and benefit attributes of adjunct-to-insulin therapies for the management of glycemic control in T1D. In the decision-making process to supplement an insulin regimen with another pharmacological agent, these results first indicate that although patients seek glycemic and weight benefits, they are most concerned about safety considerations such as the risk of DKA imposed by that therapy. Second, these results indicate that in comparing risk profiles between a lower- or higher-dose oral SGLTi and a subcutaneous therapy, or the option of maintaining therapy with insulin alone, the balance of risk and benefit shows a clear patient preference for the lesser-risk strategy of low-dose oral SGLTi.

These findings were demonstrated in this survey using different methodologies. The iterative conjoint analysis method showed that 83% of participants prefer the profile of an adjunct-to-insulin therapy such as a low-dose SGLTi, where

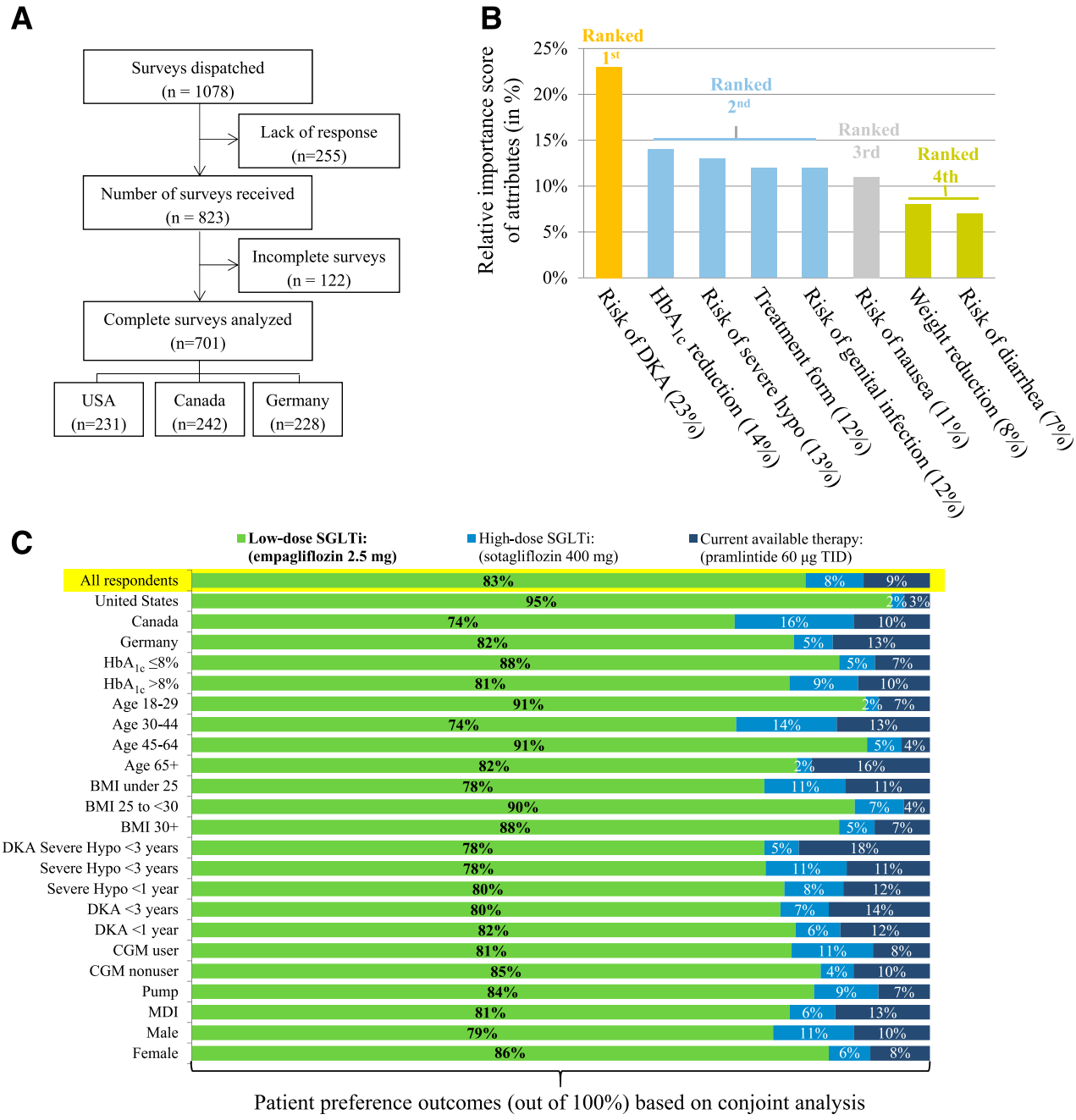

Figure 1—*A*: Flow diagram of survey responses and selection. *B*: Relative importance and ranking of attributes as determined by conjoint analysis. Relative scores expressed in % as weighted out of 100; attributes depicted with the same color are similarly important. *C*: Conjoint analysis of patient preference outcomes in the overall respondent population (highlighted in yellow) and predefined subgroups. hypo, hypoglycemia.

the risk of DKA is lower relative to the higher-dose SGLTi, and the oral route was preferred rather than the injectable route. The explicit choice method demonstrated that 69% chose a therapy profile similar to a low-dose oral SGLTi compared with the other therapies or insulin alone. The likelihood-to-adopt questionnaire indicated that 87% of participants were likely (52%) or definite (35%) regarding their decision to adopt such a therapy, with proportions much higher than for the other options. Indeed, only a minority (12%) of persons were unlikely or definitely not willing to take a low-dose SGLTi in contrast to the majority who were unlikely or definitely not willing to take high-dose SGLTi (53%) or subcutaneous injection therapy (56%) as adjunctive therapy.

This systematic approach to determining the patient voice in direct response to their review of the data from phase 3 clinical trials represents important information to be considered by patients and clinicians in the decision-making process for selecting new therapies.

Long-term glycemic control data from clinical trial participants (20) and from population-based cohort studies (2,3) demonstrate that only a small proportion of persons with T1D maintain target levels of HbA_{1c}. Therefore, therapeutic choices to supplement intensive insulin therapy would be highly desirable by

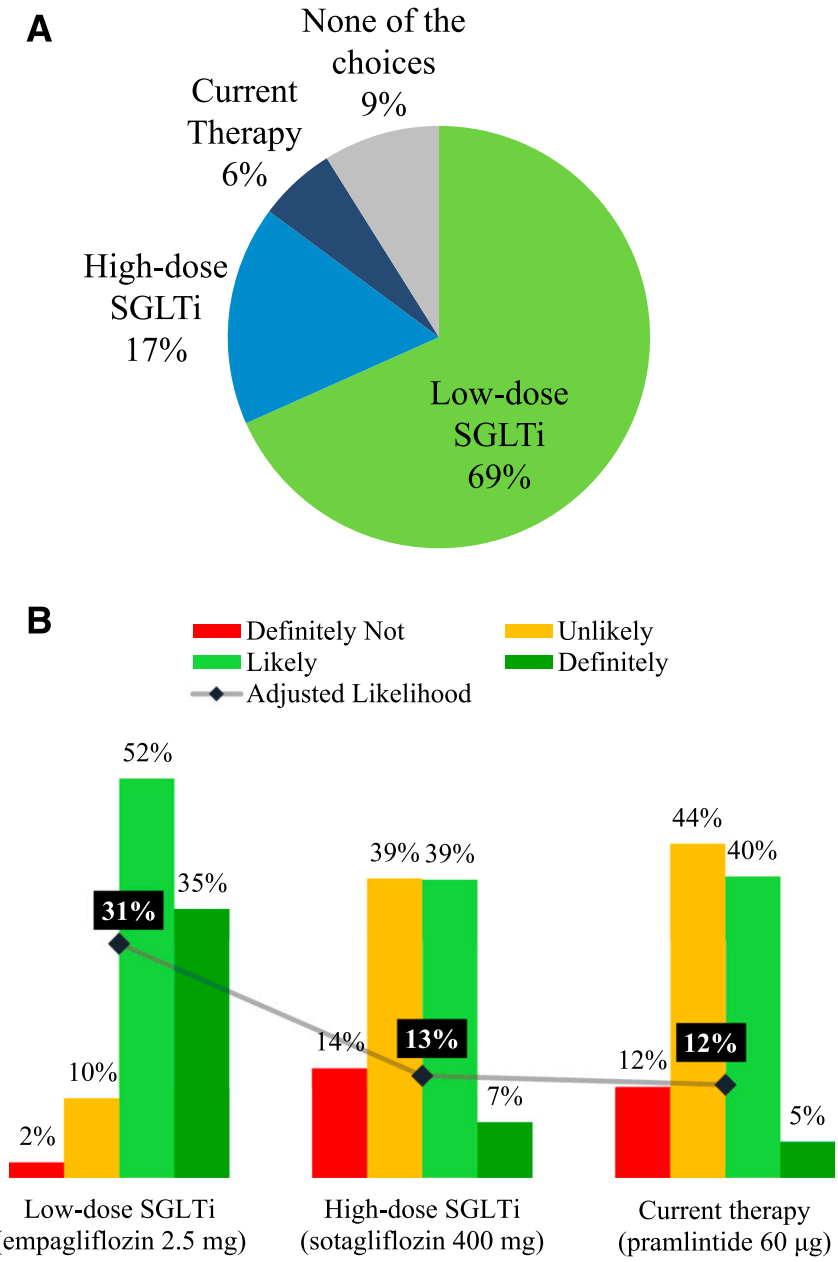

Figure 2—*A*: Explicit patient responses for preferred adjunct-to-insulin therapy choice. *B*: Explicit likelihood-to-adopt responses for the three proposed medication options; the adjusted likelihood score is defined as a weighted score represented by 50% of the "definitely" score plus 25% of the "likely" score.

clinicians and patients. The SGLTi class of medications has a clear effect on improving HbA_{1c} without an increase in rate of hypoglycemia, while showing modest weight reduction and blood pressure lowering, small decreases in insulin dose requirements, and increased time in target glucose range (6,8–10,12,21–24). Additionally, these agents have the potential benefit, based on trials in patients with T2D, to improve cardiovascular and renal outcomes (14,15,25–27).

For provision of a clear net benefit to patients, adjunctive-to-insulin therapy options should not increase the risk of adverse events in T1D. Risk minimization of acute complications in T1D is particularly important from a clinical perspective given the current observation that in clinical practice 4.8% of patients experience at least one DKA event per year and 11.8% experience at least one severe hypoglycemic event per year (28), without the use of adjunctive-to-insulin therapies. Systematic use of pramlintide therapy might be expected to increase the baseline rates of severe hypoglycemia, likely in part explaining the very low use in the U.S. despite its indication as an adjunct-to-insulin agent in T1D (5). Similarly, the systematic use of SGLTi, if approved, might be expected to increase the baseline rates of DKA, requiring specific mitigation strategies.

European regulatory approval for use of dapagliflozin in T1D in patients with BMI ≥27 kg/m^2 was gained in February 2019 and sotagliflozin in March 2019 with similar restrictions. Ipragliflozin (in December 2018) and dapagliflozin (in March 2019) also gained regulatory approval in Japan for use in T1D. Accordingly, broader clinical use of SGLTi in persons with T1D will require implementation of DKA risk mitigation plans. These should include informative drug labels for safe use of SGLTi in this setting, as well as intensive educational programs including tools such as a medication guide, prescriber-oriented and patient-oriented education and training platforms, medication alert cards, and DKA risk recognition strategies such as the smart use of capillary ketone monitoring (29,30). Finally, the use of lower-dose SGLTi, associated in clinical trials with low risk of DKA comparable to that of placebo (8), should be considered as another component of the DKA mitigation strategy. This is consistent with recent clinical perspectives on potential safe use of SGLTi in T1D in which recommendations are made for the clinical use of the lowest available dose of any efficacious agent in order to lower as much as possible the risk of DKA (16–18).

The concept of a low-dose SGLTi strategy also seems to be preferred by patients where the tradeoff for slightly lower glycemic efficacy in terms of HbA_{1c} lowering in exchange for reduced DKA risk is favored. Current results demonstrate objectively that a potential three- to fivefold increased DKA risk is of most concern and highly relevant from the patient perspective, seen as the most important attribute relative to other attributes including the potential for an HbA_{1c} lowering of nearly 0.5% (5.5 mmol/mol). The choice for the most optimal adjunct-to-insulin therapy, from a patient perspective, was therefore impacted to a large degree by the increased risk of DKA. Understanding and reducing the risk of DKA in

general is especially important given recent data indicating an increased rate of DKA in the U.S. from 2009 to 2014, since SGLTi was only first approved for use in T2D in 2013 (31).

The results of this scientific survey have several strengths. One is the objective nature of the study utilizing the well-established and validated discrete choice experiment form of conjoint analysis (19,32). The core of conjoint analysis relies on the untangling of the complex tradeoffs patients unconsciously make when selecting one drug product over another, allowing for the objective qualification of patient preferences. Based on the reliability of this unbiased analysis methodology, its use to measure patient preferences has increased in health care research where health authorities such as the U.S. Food and Drug Administration (Center for Devices and Radiological Health) also value its utility (33–36). Other strengths of the survey are the clinical applicability and relevance of the data generated, given the baseline clinical characteristics of the selected respondent population. The population studied was on different insulin regimens across a wide range of ages, with an overall glycemic control (mean HbA_{1c} of 8.5% [69 mmol/mol]) that is close to what is currently achievable in real-world care, as evidenced by the latest T1D Exchange data with a mean HbA_{1c} of 8.4% (68 mmol/mol) (2,3).

Limitations include the extent of the selection of attributes included in the conjoint analysis (limited to eight efficacy and safety outcomes in total), that the effect size of some attributes was determined from individual trials rather than a summary measure of multiple trials, and that glucose time in range was not included in the analysis. Use of glucose time in range could not be considered, as it was not evaluated for all therapies (pramlintide) and is not systematically used by all patients. Other limitations of the study include the lack of assessment of preference outcomes in patients close to or at glycemic target (HbA_{1c} $<$7.5% [$<$58 mmol/mol]) as well as the lack of inclusion of patients beyond North America and Europe. Despite these limitations, overall, the results of this scientific survey may help to better characterize the efficacy versus safety tradeoff choices and patient preferences in terms of the potential use of adjunct-to-insulin therapy options in T1D. The clear preference of patients for a low-dose oral SGLTi option as an adjunct-to-insulin therapy was quite robust using a validated method for the evaluation of preferences.

The results of this scientific survey are clinically significant at this juncture in time, given recent approvals of some SGLTi as adjunct-to-insulin therapy in T1D (thus far for sotagliflozin and dapagliflozin in Europe) and ongoing efforts elsewhere to gain regulatory approvals. These survey results will be highly informative for potential prescribers of SGLTi in T1D and their dialogue with patients in choosing an optimal and customized therapy option. These results also highlight the importance of the DKA risk with SGLTi use in T1D as a genuine concern for the patients and as a critical topic in the overall benefit-risk analysis of these new agents for T1D. There is a clear need to effectively reduce this important risk in clinical practice (once agents gain regulatory approval) where, in addition to effective DKA education measures, one important strategy to consider would be the use of a lower approved SGLTi dose.

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