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SHORT COMMUNICATION

Off-label prescription of SGLT-2 inhibitors to patients with type 1 diabetes: an online survey of diabetes specialists in Italy

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The European Medicines Agency Committee for Medical Products for Human Use (CHMP) has recently approved dapagliflozin and issued a positive opinion for sotagliflozin, as adjunctive treatments to insulin for adults with type 1 diabetes (T1D). The decisions were made based on the results of randomized clinical trials (RCT) conducted in patients with T1D (DEPICT studies for dapagliflozin and InTANDEM studies for sotagliflozin) [1, 2]. Furthermore, also empagliflozin and canagliflozin have shown positive results as adjunct treatment to insulin in patients with type 1 diabetes (EASE-2 and EASE-3 trials for empagliflozin) [3, 4]. However, there are some safety concerns for the increased risk of diabetic ketoacidosis associated with the use of these drugs in patients with T1D [1–4]. The CHMP provides a list of conditions to mitigate the risk of diabetic ketoacidosis (DKA), including patient selection (prescription by a specialist, only to patient with a BMI above 27 and excluding those with low insulin requirement), diabetes management (optimization of insulin therapy with lowering of insulin doses only to prevent hypoglycemia) and active prevention of DKA (patient education and commitment to the measurement of blood ketones). Similar recommendations were presented in details in a recent consensus published on Diabetes Care [5]. The increased risk of DKA is indeed the reason why, almost at the same time, the Food and Drug Administration (FDA) rejected sotagliflozin and, more recently, dapagliflozin as adjunct to insulin for the treatment of type 1 diabetes.

After the publication of the first encouraging results of the use of sodium glucose cotransporter 2 (SGLT-2) inhibitors in patients with T1D, there has been an increase in the off-label prescription of these drugs to patients with T1D worldwide. The aim of this study was to survey Italian specialists about the off-label prescription of SGLT-2 inhibitors to patients with T1D.

Starting August 21, 2018, the Italian Association of Clinical Diabetologists (Associazione Medici Diabetologi, AMD) invited their members to participate in an online anonymous survey on the off-label prescription of SGLT-2 inhibitors to T1D patients. The link to the online survey was sent four times to a mailing list of 2200 specialists, specifying in the

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introductive paragraph that the survey was targeting specialists who cared for patients with T1D. The questions of the survey are listed in supplementary Table 1. To estimate the number of patients prescribed SGLT-2 inhibitors by the survey participants, we used the median value when responders indicated a range of values. The survey was completed by diabetes specialists, online and in an anonymous form; therefore, there was no need for approval by an ethics committee.

Between August 21, 2018, and April 03, 2019, $n = 161$ eligible specialists (diabetologists, endocrinologists or internists) completed the survey and 44.7% of them had indeed prescribed SGLT-2 inhibitors to T1D patients. The characteristics of diabetes specialists who completed the online survey are presented in Table 1. Specialists who prescribed SGLT-2 inhibitors to T1D patients were similar to those who did not, as for years in practice and type of practice (university hospital-based clinic, hospital-based clinic, stand-alone clinic, private practice). Specialists who practiced in Northern Italy or cared for ≥ 50 T1D patients were more likely to prescribe SGLT-2 inhibitors to their T1D patients. The estimated number of T1D patients who were prescribed SGLT-2 inhibitors by the specialists who completed the survey was $n = 431$.

Table 1 Characteristics of diabetes specialists who completed the online survey and who did or did not prescribe off-label SGLT-2 inhibitors to patients with T1D

	Off-label prescription of SGLT-2 inhibitors to patients with T1D		*P* value
	Yes ($n = 72$)	No ($n = 89$)	
Years of practice as specialist			
< 10	11 (15.5%)	11 (12.4%)	0.399
10–19	17 (23.9%)	27 (30.3%)	
20–29	24 (33.8%)	21 (23.6%)	
≥ 30	19 (26.8%)	30 (33.7%)	
Geographical area of practice			
Northern Italy	44 (61.1%)	24 (27.0%)	0.001
Central Italy	13 (18.1%)	29 (32.6%)	
Southern Italy and main islands	15 (20.8%)	36 (40.4%)	
Type of facility			
Hospital-based clinic	35 (48.6%)	40 (44.9%)	0.351
Stand-alone clinic	19 (26.4%)	33 (37.1%)	
University hospital-based clinic	12 (16.7%)	7 (7.9%)	
Private clinic	4 (5.6%)	5 (5.6%)	
Clinic based in a private hospital caring for RHS patients	2 (2.8%)	4 (4.5%)	
Number of patients with T1D cared for			
< 50	13 (18.1%)	42 (47.2%)	0.001
50–199	35 (48.6%)	40 (44.9%)	
≥ 200	24 (33.3%)	7 (7.9%)	

Data are presented as frequency with proportion in parentheses

SGLT-2 Sodium glucose cotransporter 2 inhibitors, *T1D* type 1 diabetes mellitus, *RHS* regional healthcare system

The response to selected survey questions are presented in Table 2. The majority of specialists prescribed SGLT-2 inhibitors to T1D patients on MDI [MDI 61.1%, CSII 4.2%, on either form of insulin treatment 34.7%]. The three most common reasons for the prescription were to improve suboptimal glucose control, to facilitate weight loss and to decrease insulin requirement, while the three least common reasons were to improve fasting rather than postprandial glucose, to comply with patient's request and to improve blood pressure control. Only 50% of the specialists who prescribed SGLT-2 inhibitors to T1D patients asked patients to sign an informed consent for the off-label use of these drugs.

Of the specialists who prescribed SGLT-2 inhibitors to T1D patients, 25% did not prescribed strips for the measurement of ketones in either the urine or blood, and only 20.8% of them instructed patients to start checking ketones in the urine or blood when glucose levels exceed 200 mg/dl. All specialists recommended patients to avoid dehydration and prolonged fasting while taking SGLT-2 inhibitors; however, only 27.8% of the specialists reviewed with their patients the signs and symptoms of ketosis and only 9.7% provided their patients all the six recommendations suggested by experts [5] and listed in the survey (question 12). As for the off-label prescription of SGLT-2 inhibitors to adult T1D women of childbearing age, 19.4% of the specialists provided no information on the risk of taking these medications at the time of conception, with only 12.5% of the specialists provided their patients all four recommendations listed in the survey, suggested when prescribing drugs not authorized in pregnancy to women of childbearing age (question 13).

Ninety-six percent of the specialists who prescribed SGLT-2 inhibitors to T1D patients reported that their patients were satisfied with use of these drugs adjunct to insulin.

To our knowledge, this is the first report on the off-label prescription of SGLT-2 inhibitors by specialists to patients with T1D. We acknowledge that the responders to our survey may not be representative of all specialists caring for patients with T1D in Italy because of the limited number of those who completed the survey and the fact that only members of a scientific society were invited to participate. However, responders were in practice across the country, in different types of practices and with a variety of T1D patients load.

The results of the online AMD survey document the urgent need to improve the active prevention of DKA and awareness about unplanned pregnancy risks among professionals and patients when prescribing SGLT-2 inhibitors to patients with T1D. Furthermore, specialists should be encouraged to have patients sign an ad hoc informed consent

Table 2 Response to selected survey questions

Question 7. Type of insulin treatment of T1D patients prescribed SGLT-2 inhibitors	
MDI	44 (61.1%)
CSII	3 (4.2%)
Either CSII or MDI	25 (34.7%)
Question 8. Type of glucose monitoring of T1D patients prescribed SGLT-2 inhibitors	
SMBG only	24 (33.8%)
CGM only	6 (8.4%)
FGM only	7 (9.9%)
More than one type of glucose monitoring	34 (47.9%)
Question 9. Reason(s) for prescribing an SGLT-2 inhibitor to a T1D patient*	
To improve suboptimal glucose control	62 (86.1%)
To facilitate weight loss	45 (62.5%)
To decrease daily insulin requirement	39 (54.2%)
Because of the scientific evidences presented at meetings/conventions	30 (41.7%)
To reduce cardiovascular risk	19 (26.4%)
To reduce the risk of hypoglycemia	7 (9.7%)
To improve blood pressure control	6 (8.3%)
Patient's request	5 (6.9%)
To reduce fasting glucose rather than postprandial glucose	2 (2.8%)
Question 10. Use of an informed consent for the off-label prescription of an SGLT-2 inhibitor to a T1D patient:	
Yes	36 (50.0%)
No	34 (47.2%)
Do not remember	2 (2.8%)
Question 11. Availability of strips for the measurement of ketones to T1D patients prescribed an SGLT-2 inhibitor	
No	18 (25.0%)
For urinary ketones (either prior or concomitant prescription with SGLT-2 inhibitor)	14 (19.4%)
For blood ketones (either prior or concomitant prescription with SGLT-2 inhibitor)	37 (51.4%)
Do not remember	3 (4.2%)
Question 12. Recommendations to reduce the risk of ketosis*	
Abundant intake of fluids	53 (73.6%)
Avoid prolonged fasting	48 (66.7%)
Measurement of ketones during sick days	43 (59.7%)
Measurement of ketones when blood sugar is high	42 (58.3%)
Not to start a low carbohydrate diet without consulting a specialists	27 (37.5%)
Review the most common causes and symptoms of ketosis	20 (27.8%)
None of the previous recommendations	1 (1.4%)
Question 13. Recommendations/information to women of childbearing age*	
To immediately stop SGLT-2 inhibitors in case of an unplanned pregnancy	35 (48.6%)
To enter a pregnancy planning program in case the patient is considering a pregnancy	33 (45.8%)
To use effective contraception if sexually active	31 (43.1%)
The effects of the SGLT-2 inhibitors on the embryogenesis are unknown	28 (38.9%)
None of the previous recommendations/information	8 (11.1%)
Do not remember	7 (9.7%)
Question 14. Glucose threshold recommended for ketones testing (only for specialists who indeed made tools for the measurement of ketones available to patients)	
150 mg/dl	1 (2.0%)
200 mg/dl	13 (25.5%)
250 mg/dl	14 (27.4%)
300 mg/dl	7 (13.7%)
350 mg/dl	0 (0%)
No glucose threshold recommended	16 (31.4%)

Table 2 (continued)

Question 15. Patient's satisfaction with the use of SGLT-2 inhibitors as adjunct treatment to their insulin regimen	
Satisfied	69 (95.8%)
Neither satisfied or dissatisfied	1 (1.4%)
Dissatisfied	1 (1.4%)
Do not remember	1 (1.4%)

Data are presented as number of specialists who selected that specific response, with percent of specialist who responded to that specific question in parentheses. Questions indicated with an asterisk (*) allowed multiple responses

SGLT-2 Sodium glucose cotransporter 2 inhibitors, *T1D* type 1 diabetes mellitus, *MDI* multiple daily injections, *CSII* continuous subcutaneous insulin infusion, *SMBG* self-monitoring of blood glucose, *FGM* flash glucose monitoring, *CGM* continuous glucose monitoring

for the off-label prescription of SGLT-2 inhibitors in patients with T1D.

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Compliance with ethical standards

Conflict of interest Regarding the topic of this work, MS has received research grants from Lexicon and consulting fee from Sanofi Italy; for being part of a speaker's bureau, RC has received compensation from AstraZeneca Italy, PDB has received compensations from AstraZeneca Italy, Boehringer Ingelheim Italy and Mundipharma Italy and GLP has received compensations from AstraZeneca Italy and Boehringer Ingelheim Italy; FB, CM, AG, MSZ and FPT have no conflict of interests to disclose.

Ethical approval In this manuscript we report the results of survey of professionals, for which no sensitive or health data were collected from patients and no ethics committee review is required.

Human and animal rights disclosure This research involved no animals.

Informed consent For this type of study informed consent of participants was not required by current regulations.

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