

Sodium-Glucose co-transporter 2-inhibitors questionnaire: A survey amongst peers

Ebony Sciberras Giusti, Roberta Mifsud, Zachary Gauci

Background: Sodium-glucose co-transporter-2 (SGLT2) inhibitors are a relatively new class of oral antihyperglycemic agents which improve glycemic control in patients with type 2 diabetes mellitus (T2DM) by preventing reabsorption of glucose in the proximal convoluted tubules of the kidney. As their use has become widespread in both the diabetic as well as the cardiac patient population it was deemed appropriate that a survey amongst peers be designed to assess knowledge of this medication's characteristics.

Methods: An online 42 closed-ended question survey was drafted. It comprised of 7 sections, each pertaining to an important characteristic of this drug class. The survey was circulated via email to doctors in all levels of training in both primary and secondary care. .

Results: A total of 171 questionnaire responses were received. Subsequent data analysis demonstrated generalized limited awareness of the different important considerations to prescribing this medication class.

Conclusion: This study reveals that there is a need for better doctor education on SGLT2 drug class. Henceforth an informative poster highlighting the most pertinent drug characteristics and considerations was created and circulated amongst doctors.

Dr Ebony Sciberras Giusti, MD
Department of Medicine,
Mater Dei Hospital,
Msida, Malta

Dr Roberta Mifsud, MD
Department of Medicine,
Mater Dei Hospital,
Msida, Malta

Dr Zachary Gauci, MD
Department of Medicine,
Mater Dei Hospital,
Msida, Malta

Sodium-glucose co-transporter-2 (SGLT2) inhibitors are a relatively new class of oral antihyperglycemic agents which improve glycemic control in Type 2 diabetes mellitus (T2DM) by preventing reabsorption of glucose in the proximal convoluted tubules of the kidney. Their introduction has been lauded as a cornerstone in the treatment of Type 2 diabetes. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have recognized their significant cardio- and renovascular benefits placing them as first-line add-on agents, following initiation of metformin, in the management of T2DM with chronic heart failure, atherosclerotic cardiovascular disease or nephropathy.¹ This has also been reflected in the updated National Institute of Clinical Excellence (NICE) guidelines (NG28).² A multitude of cardiovascular trials have taken place over the recent years, repeatedly demonstrating SGLT2 inhibitor's ability to provide a significant reduction in cardiovascular outcomes in both diabetic and non-diabetic patients. More specifically, a reduction in heart failure hospitalizations, cardiovascular death, all-cause mortality and MACE-3 events (i.e. a composite of nonfatal stroke, nonfatal myocardial infarction and cardiovascular death) has been demonstrated in various trial results.² They have been recognized to be the sole drug to be effective across the entire LVEF spectrum of heart failure, proving to be efficacious in both chronic heart failure with preserved and reduced ejection fraction.³ Current practice guidelines advocate the following recommendations: The American Diabetes Association (ADA) recommends the addition of SGLT-2 inhibitors in the management of T2DM with HF or patients at high risk of HF.¹ The most recent European Society of Cardiology (ESC) 2021 and the American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) 2022 HF guidelines recommend the use of SGLT-2 inhibitors (currently only dapagliflozin and empagliflozin) in the management of chronic, stable HFrEF (class 1 recommendation for a reduction in cardiovascular death and HF hospitalizations) irrespective of baseline diabetes status. The AHA/ACC/HFSA HF guidelines 2022 provide a class 2A recommendation for HFrEF and HFpEF.⁴

This group of medications do however have their own adverse effects and treatment considerations. Thus, adequate knowledge of their mode of action, adverse effects, drug-drug interactions and monitoring requirements is paramount as their use becomes widespread.

These agents have been available for purchase in Malta from community pharmacies against a prescription by any registered clinician, for a number of years. In 2021, SGLT2 inhibitors in the form of empagliflozin were however introduced on the national formulary free of charge, for selected patients with type 2 diabetes mellitus meeting particular criteria. In the latter case, the initial prescribing rights are restricted to specialist diabetologists. As the cost of purchasing these medications was eliminated, the number of patients taking these agents increased. Clinicians irrespective of their specialty are thus likely to encounter these patients in their practice. It was thus felt important by the authors to explore the knowledge and awareness of this drug class amongst clinicians working in various specialties including community practice, A&E, internal medicine and surgical specialties.

MATERIALS AND METHODS

This study was carried out over a five-month period (May 2022 to September 2022). Data collection was carried out by means of a questionnaire. A standardized email demonstrating a description of the questionnaire was prepared together with a hyperlink to an online survey website (the questionnaire itself). This was sent to Medical and Surgical Departmental secretaries of both Mater Dei Hospital and Gozo General Hospital; i.e., Secondary care, for the necessary approval for dissemination. Once obtained, the email was disseminated to all members of each respective subspecialty within the department. The same process was used with regards to dissemination in Primary Healthcare, where email dissemination was carried out to each Primary Healthcare branch in both Malta and Gozo. Specialists in Endocrinology were excluded from participating.

Involved departments in Medicine included: Accident and Emergency, Cardiology, Respiratory, Gastroenterology, Geriatric Medicine, Oncology and

Palliative Care and Haematology. Involved departments in Surgery included: General Surgery, Urology, Orthopaedics, ENT, Cardiothoracic Surgery, Vascular Surgery, Anaesthesia, Obstetrics and Gynaecology.

Participation in this study was voluntary and confidentiality was guaranteed.

The respondent characteristics section included the specialty and the designation (consultant/resident specialist/higher specialist trainee/basic specialist trainee/foundation doctor). The cohort characteristics are summarized in [Table 1](#).

The questionnaire consisted of seven sections:

1. Respondent characteristics
2. SGLT2 inhibitor licensing and mode of action
3. Prescribing and patient counseling
4. Adverse Effects
5. SGLT2 and diabetic ketoacidosis
6. Drug interactions
7. Specific SGLT2 inhibitors

The questions were designed by the authors, formulating them with close consultation of the products' summary of product characteristics leaflets. Special emphasis was placed on the clinical implications of SGLT2 Inhibitors given that our studied cohort are active prescribing clinicians. The chosen questions were evaluated by two medical specialists in an attempt to ensure their validity and relevance. 980 clinicians were invited to complete the questionnaire over a 5-month period. 3 reminders

were sent over the 5-month period. 172 responses were received. No responses were excluded.

Permission was sought from the Departmental Chairperson after a readthrough of the proforma. No funding was required and no patient-specific data was collected.

RESULTS

Of the 171 questionnaires that were collected, 78 originated from doctors in primary care and 93 from doctors in secondary care. The correct response rate for primary care participants in this survey was found to be of 45% whilst that of secondary care was of 47%. For participants in secondary care, grade participation was split as per [Table 1](#). Notably 20.93% of the participants were of consultant grade, closely followed by Foundation Year Doctors at 15.7%.

The different specialties involved were as demonstrated in [Table 2](#) with Medicine being the specialty with the highest number of participants.

[Tables 3 – 8](#) describes the question content and correct response rate per question.

- Licensing and MOA: overall correct response rate: 51% (Mean 38.78, SD 34.71) ([Table 3](#))
- Prescribing and Patient Counseling: overall correct response rate: 33% (Mean 47.11, SD 29.38) ([Table 4](#))
- Adverse Effects: overall correct response rate: 39% (Mean 55.62, SD 32.65) ([Table 5](#))

Table 1 Grade of Participants

Grade	Percentage
Consultant	21%
Resident Specialist	8%
Higher Specialist Trainee	15%
Basic Specialist Trainee	11%
Foundation Year Doctor	16%
General Practitioner	5%
Specialist GP	15%
GP Trainee	9%

Table 2 Participating departments according to responding frequency (%)

Department	Percentage
Medicine	45%
General Practice	43%
Accident and Emergency	39%
Surgery	29%
Unspecified	7%
Cardiology	6%
Anaesthesia	1%
Obstetrics and Gynaecology	1%

- SGLT2 inhibitors and DKA: overall correct response rate: 26% (Mean 28.32, SD 22.64) (Table 6)
- Interactions: overall correct response rate: 31% (Mean 43.50, SD 29.88) (Table 7)
- Specific SGLT2 inhibitors: overall correct response rate: 25% (Mean 29.46, SD 26.54) (Table 8)

The overall correct response rates per subsection were as summarized below and demonstrated in Figure 1.

The weakest data field was that of Specific SGLT2 Inhibitors, while the strongest data field was of Licensing and Mode of Action. However,

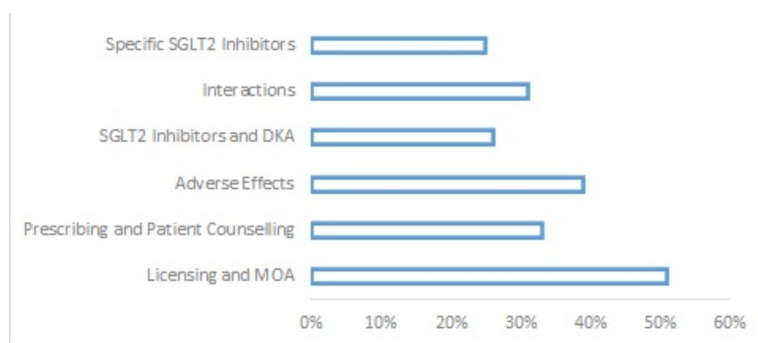


Figure 1 Correct Response rate per subsection

Table 3 Licensing and Mode of Action

Question	Description	Correct response (%)
4	SGLT2 inhibitors licensing in patients with chronic heart failure	18.90%
5	SGLT2 inhibitors licensing in patients with diabetes mellitus	9.60%
6	SGLT2 inhibitors mode of action on the kidneys	78.40%
7	SGLT2 inhibitors mode of action on insulin	6.50%
8	SGLT2 inhibitors effect on blood pressure and weight	11.29%
9	SGLT2 inhibitor effects on cardiovascular outcomes	83.87%
10	SGLT2 inhibitors effect in patients with chronic kidney disease	62.90%

Table 4 Prescribing and patient counselling

Question	Description	Correct response (%)
11	SGLT2 inhibitors method of administration	64.49%
12	Renal profile monitoring when taking SGLT2 inhibitors	7.48%
13	SGLT2 inhibitors effect on HbA1c levels	58.49%
14	Dapagliflozin dosing	22.43%
15	Empagliflozin dosing	19.81%
16	SGLT2 inhibitors effect in severely unwell hospitalized patients	18.69%
17	SGLT2 inhibitors administration prior to major surgical intervention	36.19%
18	Considering euglycaemic DKA in unwell patients who are taking SGLT2 inhibitors	82.24%
19	The need for counselling patients regarding the risk of euglycaemic DKA whilst taking SGLT2 inhibitors	80.95%
20	SGLT2 inhibitors prescription in patients with recurrent urinary tract infections	80.37%

Table 5 Adverse Effects

Question	Description	Correct response (%)
21	SGLT2 inhibitors in pregnancy	7.62%
22	SGLT2 inhibitors side effects	76.19%
23	Diuretic mechanism of SGLT2 inhibitors	76.19%
24	Orthostatic hypotension as an adverse effect of SGLT2 inhibitors in at risk patients	62.50%

Table 6 SGLT2 inhibitors and DKA

Question	Description	Correct response (%)
25	Likelihood of DKA in patients administering SGLT2 inhibitors	11.34%
26	Biochemical picture of DKA in patients administering SGLT2 inhibitors	6.25%
27	Risk of DKA in the context of SGLT1 inhibitor use in patients with a carbohydrate rich diet	28.13%
28	Insulin dosage changes and development of DKA in patients administering SGLT2 inhibitors	39.58%
29	Predisposing factors for DKA development in patients administering SGLT2 inhibitors	68.04%
30	Administration of SGLT2 inhibitors during DKA	4.12%
31	Recommencing SGLT2 inhibitor administration upon DKA resolution	19.59%
32	Pancreas insulin production as a risk factor for DKA	49.48%

Table 7 Interactions

Question	Description	Correct response (%)
33	Co-prescription SGLT2 inhibitors with diuretics	38.30%
34	Commencement of SGLT2 inhibitors in patient with Type 2 diabetes mellitus	59.57%
35	SGLT2 inhibitors hypoglycaemic effect in comparison to sulfonylureas	7.45%
36	SGLT2 inhibitors and renal impairment	41.94%
37	SGLT2 inhibitors effect on insulin induced weight gain	4.26%
38	Diuretic, antihypertensive and SGLT2 inhibitor co-prescribing	71.28%
39	Oral hypoglycaemic agents, insulin dosing and SGLT2 inhibitor co-prescribing	81.72%

Table 8 Specific SGLT2 inhibitors

Question	Description	Correct response (%)
40	Canagliflozin and lower limb amputations risk	26.64%
41	Eligibility criteria for empagliflozin via government formulary	57.30%
42	SGLT2 inhibitor entitlement requirements	4.44%

percentage correct was highest at only 51% correct response rate in the Licensing and Mode of Action subsection. For each subsection, participants had the option to answer True/False/I don't know and had the option to skip. With regards to skipped questions, a comparative figure of the average number of skipped questions per section is shown in [Figure 2](#). With respect to specific questions, the weakest recorded response rate was Question No. 11: "SGLT2 Inhibitors can be taken once daily ideally after the first meal", at 6% correct response rate. According to the summary of product characteristics, SGLT2 inhibitors are taken prior to the first meal. The question which generated the highest correct response rate was Question No. 9: "SGLT2 inhibitors have beneficial cardiovascular effects: decreasing heart failure hospitalization and reducing incidence of cardiovascular death", at 60% correct response rate.

DISCUSSION

To the best of the authors' knowledge, this study is the first of its kind to attempt evaluating clinicians' (specifically non-endocrinologists) understanding of SGLT2 inhibitors locally. SGLT2 inhibitors have only been introduced on the local hospital formulary relatively recently. The results show limited knowledge in all 7 seven domains of our questionnaire.

The mode of action of SGLT2 inhibitors and their beneficial effects seem to be known by the majority of participants. Knowledge in other domains is however notably lacking and needs addressal. There is a lack of awareness of the specific characteristics of these medications ranging from licensing details up to interactions with other medications. Of particular

clinical concern is the suboptimal response rate in the patient safety section.

Specific concerns arise when reviewing the results obtained from the section titled "SGLT2 Inhibitors and DKA". Unfortunately, the results indicate that there needs to be more awareness regarding the predisposing risk factors as well as the implications these medications have on the risk of diabetic ketoacidosis.

The design of the questionnaire was such that as the questions progressed, they became gradationally more specialized and specific as reflected in the incrementally increasing number of skipped and "I don't know" responses per subsection. This implies that, generally, a basic understanding of SGLT2 inhibitors' mode of action and the most common side effects can be assumed, however important in-depth knowledge as per the stipulated subsections is lacking. The low correct percentage response rate in the final section titled "Specific SGLT2 Inhibitors" was expected given this questionnaire did not involve specialist endocrinology consultants or trainees.

The fact that 5 out of 6 subsections scored a correct response rate of below 40% demonstrates the need to better equip and empower clinicians in Malta with knowledge on these medications. This is paramount, as these medications are now part of the treatment guidelines for both diabetes mellitus type 2 and congestive heart failure, both of which are increasingly prevalent in the Maltese population.

Limitations

The suboptimal participation rate is a limitation in this study. Henceforth care needs to be taken before generalizing the results of this study. The number of incorrect responses however still raise concern about the limited knowledge of SGLT2 inhibitors and the potential negative effects on patients, validating the need for the aforementioned recommendations. Question bias could pose as a possible weakness in this questionnaire as it was not tested for reliability. The questionnaire did not specifically cover genitourinary tract infections as an adverse effect of SGLT2 inhibitor use.

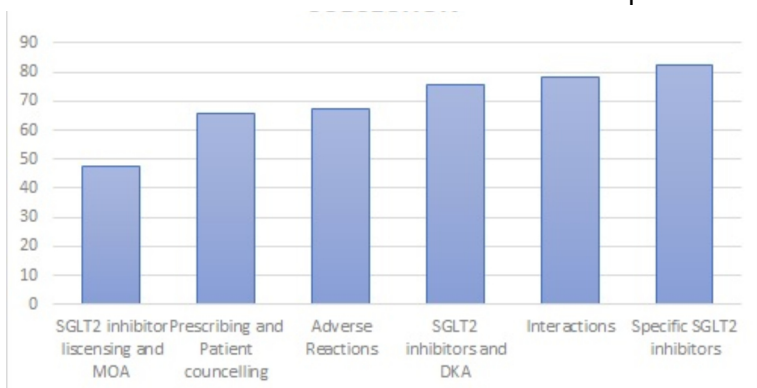


Figure 2 Average Skipped Questions per Subsection

RECOMMENDATIONS

In response to the results, the following recommendations are being put forward:

- To organize medical update meetings involving general practitioners as well as doctors in secondary care.
- To involve more clinical pharmacists in the wards.
- To create up-to-date clinical practice guidelines outlining diabetes sick day rules and medication modification guidance.

CONCLUSION

There is an important role for the use of SGLT2 inhibitors in the management of type 2 diabetes mellitus and chronic heart failure, and their use in these conditions is becoming increasingly prevalent. Thus, adequate knowledge on the specifics of this drug class is paramount. This questionnaire demonstrates that it is necessary to raise awareness on these medications, across all grades and specialties in both primary and secondary care.

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