Non-Interventional Study Report

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Prospective Diabetes Registry of Patients with Type 2 Diabetes Mellitus on SGLT2 Inhibitor Therapy in Singapore

Sponsor: AstraZeneca

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LIST OF ABBREVIATIONS

Abbreviations

Abbreviation or special term	Explanation
BMI	Body Mass Index
FPG	Fasting Plasma Glucose
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
PPG	Post Prandial Glucose
SGTL2i	Sodium-Glucose Transport Protein 2 inhibitors
T2DM	Type 2 Diabetes Mellitus

STUDY REPORT SUMMARY (ABSTRACT)

Prospective Diabetes Registry of Patients with Type 2 Diabetes Mellitus on SGLT2 Inhibitor Therapy in Singapore

Background/Rationale:

T2DM is associated with overweight/obesity and high fasting plasma glucose (FPG) in White patients, whereas Asian patients are more predisposed to high abdominal fat distribution and high postprandial glucose (PPG) levels. In response to identical meals, Asian subjects exhibit greater glycemic response than White subjects.According to the Diabetic Society of Singapore, one out of nine people aged 18 to 69 has diabetes which corresponds to about 11.3% of the population or more than 400,000 people, and this is expected to rise with the increasing prevalence of a sedentary lifestyle and high-calorie dietary intake.

SGLT2 inhibitors offer a novel insulin-independent approach to lower hyperglycaemia and improve metabolic control of T2DM. They reduce renal glucose reabsorption by inhibition of SGLT2 transporters in the proximal tubule of the kidney, resulting in urinary glucose excretion. Since SGLT2 inhibition is independent of β-cell function or insulin sensitivity, this treatment approach could have applications throughout the natural history of diabetes.

The reductions in FPG concentration and bodyweight during the treatment with the SGLT2i are sustained. Early weight loss is partly due to a mild osmotic diuresis caused by SGLT2i; however, the gradual progressive reduction in bodyweight thereafter, with decreased waist circumference, is consistent with a reduction of fat mass. This reduction is potentially attributable to the loss of excess energy through glucose excretion in the urine, an effect supported by the increased urinary glucose/creatinine ratio in patients assigned to SGLT2i.

Many trials have shown that SGLT2i can improve glycaemic control in patients who have inadequate control with metformin. The drug acts independently of insulin, lowers weight, and is not associated with risk of hypoglycaemia. Safety and tolerability of the drugs were also confirmed. Therefore, addition of SGLT2i to metformin provides a new therapeutic option for treatment of type 2 diabetes.

Objectives and Hypotheses:

To assess the change in HbA1c during the 1year follow-up [Time Frame: day 0, 52 weeks]

- Change of HbA1c from baseline to the end-point. [Time Frame: day 0, 52 weeks]
- Percentage of patients reaching the target of HbA1c <7.0% at end of 52 weeks

Secondary Objectives:

All assessments were done at 52 weeks

- To estimate the change in fasting plasma glucose (FPG) [Time Frame: day 0, 52 weeks]
- To estimate the change in weight (in kilograms) [Time Frame: day 0, 52 weeks]

- To estimate the change in BMI in kg/m2 [Time Frame: day 0, 52 weeks]
- To estimate the change in blood pressure (systolic/diastolic, in mmHg) [Time Frame: day 0, 52 weeks]
- To estimate the change in lipids (Total Cholesterol, HDL, LDL and triglycerides, in mmol/L) [Time Frame: day 0, 52 weeks]
- To estimate the change in serum creatinine [Time Frame: day 0, 52 weeks]
- To estimate the changes in waist circumference (in centimetre) [Time Frame: day 0, 52 weeks]
- To assess the hypoglycaemic events (including minor and major events) [Time Frame: day 0, 52 weeks]

Methods: This was a non- interventional, observational, multicenter, retrospective (existing patients on SGLT2i), and prospective study from day 1 (for new patients initiated with SGLT2i therapy), to evaluate real life clinical effectiveness and safety of SGLT2 inhibitors in Singaporean Type 2 diabetes mellitus patients treated on an outpatient basis in clinical practice setting.

Patients who satisfied the following eligibility criteria were enrolled in the study:

Inclusion Criteria:

Outpatient ≥18 years of age

a) Diagnosed as T2DM and treated with antidiabetic medicines for at least 3 months and suitable for SGLT2 inhibitor as current treatment judged by PI with HbA1c >7.0 %
b) Will provide completed and signed written informed consents
c) Each participating investigator was asked to recruit a fixed number of patients ranging from 10 to 40 depending on site specificities.

Exclusion Criteria:

a) Hypersensitivity to any SGLT2 inhibitor or any of the components in the formulation
b) Patients with Type 1 diabetes
c) Female patients with gestational diabetes during pregnancy
d) Female patients who are pregnant, intending to become pregnant or breastfeeding
e) Severe medical condition(s) that in the view of the investigator prohibits participation in the study e.g. cancer, end stage liver disease, end stage renal failure (non-diabetes related)
f) Use of other investigational drugs at the time of enrolment
g) Renal Function: <30ml/min/1.73m²

Results:

A total of 210 patients visiting general and private practitioners in Singapore were enrolled for this study.

The mean age of the study population was 54.82 ±11.34 years, and majority (65.24%) of participants were males. Majority of the participants were non-smokers (71.43%) and never consumed alcohol (68.57%). Hypertension and dyslipidaemia were the commonest underlying disorders. Duration of diabetes was over 10 years in majority of the study participants (47.14). The mean total cholesterol, HDL and LDL levels were within normal limits while the mean triglyceride level was on the higher side. The mean FPG and the HbA1c levels were also high.

A significant decrease in the mean HbA1c level was noted at the end of 52 weeks ($p < .0001$). A significant difference in SBP, DBP, weight, BMI and waist circumference were noted at the end of week 52 (Table 6-8). Although non-significant, a reduction in other parameters including serum creatinine, FPG and cholesterol levels was noted. A total of 99 adverse events (AEs) including 6 serious adverse events (SAEs) were reported in 60 patients (28.6%). Among these, a definite relation to the study drug was reported in 2 cases (2.02%). There were no major hypo/hyperglycaemic events reported.

Conclusion:

The outcomes of the current study suggest that SGLT2i are relatively effective in T2DM patients and brings about a significant decrease in HbA1c levels. Considerable reduction in weight, BMI, waist circumference, cholesterol and blood pressure levels were also noted. Although associated with a few of commonly known adverse effects, based on the widely available safety data, SGLT2i can be considered an effective option in T2DM.

AMENDMENT HISTORY

Amendment 1	Revision of time points from months/years to weeks. i.e. 6 months changed to 24 weeks, 1 year changed to 52 weeks and 2 years to 104 weeks. And, the visit window period was changed from 1 week before the visit to + 2 months
Amendment 2	Duration of study was reduced from 2 years to 1 year and sample size was reduced from 600 to 200.

MILESTONES

Milestone	Date
First patient enrolled	Oct 2015
Last patient completed	May 2019

1. BACKGROUND AND RATIONALE

1.1 Background and Rationale

Type 2 diabetes mellitus (T2DM) is associated with overweight/obesity and high fasting plasma glucose (FPG) in White patients, whereas Asian patients are more predisposed to high abdominal fat distribution and high postprandial glucose (PPG) levels (1-4). In response to identical meals, Asian subjects exhibit greater glycemic response than do White subjects (4,5).According to the Diabetic Society of Singapore, one out of nine people aged 18 to 69 has diabetes which amounts to about 11.3% of the population or more than 400,000 people. This is expected to rise with the increasing prevalence of a sedentary lifestyle and high-calorie dietary intake.

Sodium-glucose transport protein 2 inhibitors (SGLT2i) offer a novel insulin-independent approach for lowering hyperglycaemia and improving metabolic control of T2DM. They reduce renal glucose reabsorption by inhibition of SGLT2 transporters in the proximal tubule of the kidney, resulting in urinary glucose excretion. Since SGLT2 inhibition is independent of β-cell function or insulin sensitivity, this treatment approach could have applications throughout the natural history of diabetes (6).

The reductions in fasting plasma glucose concentration and bodyweight during the treatment with the SGLT2i are sustained. Early weight loss is partly due to a mild osmotic diuresis caused by SGLT2i. However, the gradual progressive reduction in bodyweight thereafter, with decreased waist circumference, is consistent with a reduction of fat mass. This reduction is potentially attributable to the loss of excess energy through glucose excretion in the urine, an effect supported by the increased urinary glucose/creatinine ratio in patients assigned to SGLT2i (6).

Many trials have shown that SGLT2i can improve glycaemic control in patients who have inadequate control with metformin. The drug acts independently of insulin, lowers weight, and is not associated with risk of hypoglycaemia. Safety and tolerability of the drugs were also confirmed. Therefore, addition of SGLT2i to metformin provides a new therapeutic option for treatment of type 2 diabetes (6).

2. OBJECTIVES AND HYPOTHESES

2.1 Primary Objective

To assess the change in HbA1c during a period of 1year [Time Frame: day 0, 52 weeks]

- Change of HbA1c from baseline to the end-point. [Time Frame: day 0, 52 weeks]
- Percentage of patients reaching the target of HbA1c <7.0% at end of 52 weeks

2.2 Secondary Objectives

All assessments were done at 52 weeks

- To estimate the change in fasting plasma glucose (FPG) [Time Frame: day 0, 52 weeks]
- To estimate the change in weight (in kilograms) [Time Frame: day 0, 52 weeks]

- To estimate the change in BMI in kg/m2 [Time Frame: day 0, 52 weeks]
- To estimate the change in blood pressure (systolic/diastolic, in mmHg) [Time Frame: day 0, 52 weeks]
- To estimate the change in lipids (Total Cholesterol, HDL, LDL and triglycerides, in mmol/L) [Time Frame: day 0, 52 weeks]
- To estimate the change in serum creatinine [Time Frame: day 0, 52 weeks]
- To estimate the changes in waist circumference (in centimetre) [Time Frame: day 0, 52 weeks]
- To assess the hypoglycaemic events (including minor and major events) [Time Frame: day 0, 52 weeks]

2.3 Exploratory Objective

None.

3. METHODOLOGY

3.1 Study Design – General Aspects

This was a non- interventional, observational, multicenter, retrospective (existing patients on SGLT2i), and prospective study from day 1 (for new patients initiated with SGLT2i therapy), to evaluate real life clinical effectiveness and safety of SGLT2 inhibitors in Singaporean Type 2 diabetes mellitus patients treated on an outpatient basis in clinical practice setting. The study also assessed treatment patterns with SGLT2 inhibitor patient relevant outcomes in whole population as well as pre identified patient subgroups.

The patients who in the judgment of the physician would benefit from SGLT2 inhibitor in either monotherapy or combination with other antidiabetic therapy were eligible to enter this study. All relevant information were collected from the patients after they signed the informed consent.

The details are provided in Figure 1 and Table 3-1.

Figure 1 Study Flow Chart

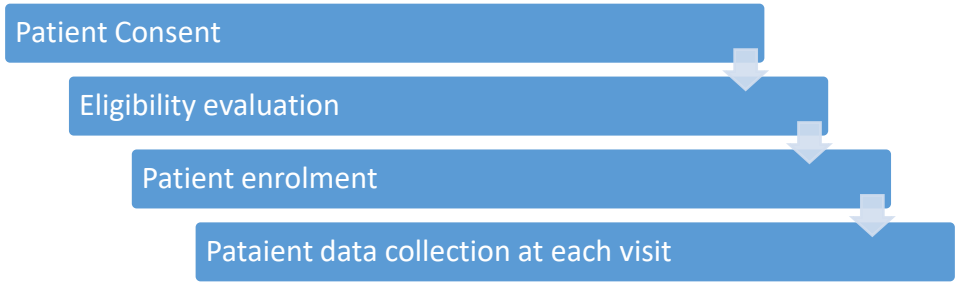


Table 3-1 Schedule of Events

Period	**Baseline**	**Follow up visits**		
Visit	1	2	3	4
Weeks	0	24 weeks	52 weeks	104 weeks
Day[1]	1	168	364[2]	728[3]
Sign Informed Consent	X			
Inclusion/Exclusion Criteria	X			
Demographic	X			
Medical History	X			
Physical Examination (weight, blood pressure, BMI, waist circumference)	X	X	X[2]	X[2]
HbA1c* & FPG*	X	X	X[2]	X[2]
Lipids (Total Cholesterol, HDL, LDL and triglycerides) & Creatinine*	X	X	X[2]	X[2]
Hypoglycaemic Events	X	X	X	X
Anti-hypertension Medication	X	X	X[2]	X[2]
Anti-Diabetic Medication	X	X	X[2]	X[2]
Anti-Lipid Medication	X	X	X[2]	X[2]
Concomitant Medication	X	X	X[2]	X[2]
Adverse events		X	X	X
End of Study Information	X	X	X[2]	X[2]

1. All patients were screened during all visits on the designated day or as close to it as possible.
2. Assessment were carried out even after the patient discontinued observational drug.

*The visit window period is + 2 months

Rationale for Study Design

There are about 14 general practitioners (GPs) and specialist medical centres in Singapore. Considering the feasibility and reliability, this study was conducted in these 14 centres and 210 adult outpatients with T2DM were enrolled. The patients were being managed with either monotherapy or combinational therapies, and in the judgment of the physician would benefit from SGLT2 inhibitor in either monotherapy or combination with another antidiabetic treatment were enrolled. This was a multicenter, non-interventional study with non-probability sampling. Therefore, results are summarised using appropriate descriptive statistics.

3.1.1 Data Source

As this was a non- interventional, observational, multicentre, retrospective (existing patients on SGLT2i), and prospective study, data were collected from each visit according to study protocol for each patient. Raw data was collected on CRF. Data pertaining to the laboratory results were entered in the respective section of the CRF.

3.1.2 Study Procedures

Following procedures were performed after the patient provided informed consent and upon confirmation of eligibility criteria.

- Following data was collected from all consented patients as available after consenting at baseline.
    - Demographic data such as age, gender, weight, height, waist circumference, and ethnic background were captured.
    - Medical history and clinical presentation
    - Duration of Diabetes
    - Laboratory data as available
    - Glycemic events encountered by patients
    - Current treatment given by the doctor

Patients were followed up as per the scheduled visits in protocol, i.e. 24 weeks, 54 weeks and 104 weeks. Following data was collected during visits

- Physical examination
- Lab tests data as available
- Glycemic events from last visit to this visit
- Treatment status
- Adverse events, if any reported by patients

3.2 Ethics

The study did not pose any risk to the patients as it is a non-interventional study. The study was performed in accordance with ethical principles that are consistent with International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements in the country.

The final study protocol, final version of the Informed Consent Form (ICF) and its translation, and CRF for the study were approved in writing by an Ethics Committee as appropriate. The study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics. The principal investigator(s) at each centre ensured that the patient was given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients were notified that they were free to discontinue from the survey at any time. The patients were given the opportunity to ask questions and allowed time to consider the information provided. The patients's signed and dated informed consent was obtained before conducting any procedure specifically for the study.

3.3 Study Population

Considering the feasibility and reliability, this study was conducted in these 14 centres and approximately 210 adult outpatients with T2DM were enrolled. Patients who gave written informed

consent and met all inclusion/exclusion criteria were enrolled in the study. The inclusion and exclusion criteria presented below are as in the study protocol.

3.4 Inclusion Criteria

- Outpatient ≥18 years of age
- Diagnosed as T2DM and treated with antidiabetic medicines for at least 3 months and suitable for SGLT2 inhibitor as current treatment judged by PI with HbA1c >7.0 %
- Will provide completed and signed written informed consents

3.5 Exclusion Criteria

- Hypersensitivity to any SGLT2 inhibitor or any of the components in the formulation
- Patients with Type 1 diabetes
- Female patients with gestational diabetes during pregnancy
- Female patients who are pregnant, intending to become pregnant or breastfeeding
- Severe medical condition(s) that in the view of the investigator prohibits participation in the study e.g. cancer, end stage liver disease, end stage renal failure (non-diabetes related)
- Use of other investigational drugs at the time of enrolment
- Renal Function: <30ml/min/1.73m²

3.6 Criteria for Discontinuation

Patients could be discontinued from study assessments at any time. Specific reasons allowed for discontinuing a patient from this study were:

• Voluntary discontinuation by the patient who was at any time free to discontinue his/her participation in the study, without prejudice to further treatment.

• Safety reasons as judged by the investigator and/or AstraZeneca.

4. VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS

4.1 Exposure

This was a non-interventional, observational study, the prescribed drugs were bought by patients. AstraZeneca did not supply any drugs/medication for this study. The medications prescribed were at the sole discretion of the physician. Information regarding current use of other mediation other than SGLT2i during the study was captured in the CRF.

4.2 Outcomes

4.2.1 **Primary Outcomes**

- Change in HbA1c during the 52 weeks follow-up

4.2.2 Secondary Outcomes

- Change in fasting plasma glucose (FPG),
- Percentage of patients reaching the target of HbA1c <7.0% at the end-point
- Change in weight (in kilograms)
- Change in blood pressure (systolic/diastolic, in mmHg)
- Change in lipids (Total Cholesterol, HDL, LDL and triglycerides, in mmol/L)
- Change in serum creatinine
- Change in BMI (in kg/m2)
- Change in waist circumference (in centimetres)
- Frequency of Hypoglycaemic events (major and minor)
    - ✓ Major - An event requiring external assistance for recovery (hospitalization)
    - ✓ Minor – An event which can be self-treated

Description of Outcome Variables in Relation to Objectives

The primary objective of this study was to study the HbA1c outcomes among the study population.

The secondary objectives were:

- To estimate the change in fasting plasma glucose (FPG) [Time Frame: day 0, 52 weeks]
- To estimate the change in weight (in kilograms) [Time Frame: day 0, 52 weeks]
- To estimate the change in BMI in kg/m 2 [Time Frame: day 0, 52 weeks]
- To estimate the change in blood pressure (systolic/diastolic, in mmHg) [Time Frame: day 0, 52 weeks]
- To estimate the change in lipids (Total Cholesterol, HDL, LDL and triglycerides, in mmol/L) [Time Frame: day 0, 52 weeks]
- To estimate the change in serum creatinine [Time Frame: day 0, 52 weeks]
- To estimate the changes in waist circumference (in centimetre) [Time Frame: day 0, 52 weeks]
- To assess the hypoglycaemic events (including minor and major events) [Time Frame: day 0, 52 weeks]

4.3 Other Variables and Covariates

Not Applicable

5. STATISTICAL ANALYSIS

5.1 Statistical Methods – General Aspects

The approach to the statistical analysis in this study was descriptive in nature. Continuous data were described by mean, standard deviation, median, minimum and maximum. Categorical data were described by the number and percentage of patients in each category.

Description of Analysis Sets

All of the enrolled population constituted study population. Full analysis set (FAS) was used for the analyses of the primary and secondary outcomes, demographics, and other variables of the study.

5.1.1 Analysis of Primary Endpoint Variables

- Change in HbA1c during the 52 weeks follow-up

5.1.2 Analysis of Secondary Variables

- Change in fasting plasma glucose (FPG)
- Percentage of patients reaching the target of HbA1c <7.0% at the end-point
- Change in weight (in kilograms)
- Change in blood pressure (systolic/diastolic, in mmHg)
- Change in lipids (Total Cholesterol, HDL, LDL and triglycerides, in mmol/L)
- Change in serum creatinine
- Change in BMI (in kg/m2)
- Change in waist circumference (in centimetres)
- Frequency of Hypoglycaemic events (major and minor)
    - ✓ Major - An event requiring external assistance for recovery (hospitalization)
    - ✓ Minor – An event which can be self-treated

5.1.3 Exploratory Objective

None.

5.2 Bias

5.2.1 Methods to Minimize Bias

All the patients treated as per the standard of care. No study drug was provided by sponsor of the study to patients.

5.2.2 **Adjustment for Multiple Comparisons**

Not Applicable

5.3 Sample Size and Power Calculations

Given that there were approximate 20 general practitioners (GPs) and specialist medical centres in Singapore, and considering the feasibility and reliability, this study was planned to be conducted in these 20 centres and approximately 600 adult outpatients with T2DM were planned to be enrolled. Changes in the conduct of the Study and Planned analyses

Initial sample size of the study was estimated to be 600. However due to slow recruitment and availability of alternative evidence like CV REAL studies, it was decided to do a protocol amendment and close the study with the number patients already recruited (210).

No interim analysis was performed as planned

Not all the patients were followed for 104 weeks as planned in the protocol.

5.4 Data Quality

Patients not meeting the inclusion/exclusion criteria for a study were not enrolled into the study and there were no exceptions to this rule. As the current study is a non-interventional study, hence there were no requirement of performing a safety follow-up.

Raw data were collected on paper CRF by the Investigator/designated investigator staff from the source documents. The CRF had pre-defined parameters for facilitation of data entry. In order to ensure Patient’s confidentiality, each patient was identified by a unique patient ID in all data and documents submitted to AstraZeneca or its representative. Data pertaining to the laboratory results was entered in the corresponding section of the CRF.

6. RESULTS

6.1 Study Participation

6.1.1 Disposition of Patients

Table 6-2

A total of 210 patients visiting general and private practitioners in Singapore were enrolled for this study. Details of patient disposition are given in Table 6-2

Table 6-2 Disposition of patients

	All Enrolled (N=210)
Total no. of patients completed the study, n (%)	
Yes	116 (55.24)
No	77 (36.67)
Unknown	17 (8.1)
Total no. of patients discontinued the study, n (%)	77 (36.67)
Reason for discontinuation, n (%)	
Adverse-events related (Please state related AE)	5 (2.3)
Lost to follow up	7(3.3)
Others (sponsor decision)	43 (20.5)
Participant's decision	3 (1.42)
Patient Deceased	1 (0.5)

All enrolled = Total number of patients consented;
Percentage is calculated using number of enrolled patients as the denominator

6.1.2 Protocol Deviation

6.2 Main Results

6.2.1 Demographic Characteristics

Demographic information of the study population has been given in Table 6-3 below in detail. The mean age of the study population was 54.82 ±11.34 years, and majority (65.24%) of participants were males.

Table 6-3 Demographic Information (Full Analysis Set)

Parameters Recorded	FAS (N=210)
Age (Year), n	208
Mean (SD)	54.82 (±11.34)
Median (Min, Max)	56 (27,90)
Gender, n (%)	209
Female	72 (34.29)
Male	137 (65.24)
Height (cm), n	206
Mean (SD)	165.16 (±33.01)
Median (Min, Max)	165.5 (145, 193)
Weight (kg), n	210
Mean (SD)	82.35 (±39.10)
Median (Min, Max)	79.9 (47.7, 132.5)
Waist Circumference (cm), n	68
Mean (SD)	102.62 (±48.75)
Median (Min, Max)	103.45 (62, 137)
BMI (kg/m2), n	151
Mean (SD)	30.23 (±14.46)
Median (Min, Max)	29.25 (19.35, 49.80)

Max = Maximum, Min = Minimum, n = Number of patients, S.D = Standard Deviation, cm = centimeter

6.2.2 Baseline Characteristics

6.2.2.1 Vital Information of Study Patients

Vital information details of the enrolled patients are listed in Table 6-4 below. Data revealed that blood pressure of patients of FAS were within normal range.

Table 6-4 Vital Information (Full Analysis Set)

Vital Parameters	**FAS (N=210)**
Resting Blood pressure (mmHg)	
Systolic	
N	179
Mean (SD)	133 (±49.59)
Median (Min, Max)	130 (94,195)
Missing	31
Diastolic	
N	176
Mean (SD)	79 (±30.48)
Median (Min, Max)	80 (59,111)
Missing	34

Max = Maximum, Min = Minimum, n = Number of patients, S.D = Standard Deviation

6.2.2.2 Summary of Personal and Medical History of Study Patients

Personal and medical history of the study participants along with diabetes duration has been provided in detail in Table 6-5. Majority of the participants were non-smokers (71.43%) and never consumed alcohol (68.57%). Hypertension and dyslipidaemia were the commonest underlying disorders. Duration of diabetes was over 10 years in majority of the study participants (47.14%).

Table 6-5 Personal and Medical History (Full Analysis Set)

Parameters	**FAS (N=210)**
Smoking n (%)	
Current	20 (9.52)
Former	25 (11.90)
Never	150 (71.43)
Unknown	15 (7.14)
Alcohol Consumption n (%)	
Current	36 (17.14)
Former	10 (4.76)
Never	144 (68.57)

Parameters	FAS (N=210)
Unknown	20 (9.52)
Medical History n (%)	
Dyslipidemia	182 (86.67)
Hypertension	162 (77.14)
Coronary Artery Disease	74 (35.24)
Cerebrovascular disease	8 (3.81)
Nephropathy	32 (52.24)
Diabetes Duration n (%)	
< 1year	8 (3.81)
1-5 years	47 (22.38)
5-10 years	53 (25.24)
>10 years	99 (47.14)
Unknown	3 (1.34)

6.2.2.3 Laboratory Investigation Results of Study Patients

The baseline levels of different parameters recorded at the onset of the study have been given in Table 6-6 below. The mean total cholesterol, HDL and LDL levels were within normal limits while the mean triglyceride level was on the higher side. The mean FPG, HbA1c and serum creatinine levels were also high.

Table 6-6 Laboratory Investigation (Full Analysis Set)

Parameters	FAS (N=210)
LIPID PROFILE	
Total Cholesterol (mmol/L)	
N	153
Mean (SD)	5.15 (±3.14)
Median (Min, Max)	4.43 (1.75, 15.04)
Missing	57
HDL Cholesterol (mmol/L)	
N	154
Mean (SD)	1.36 (±0.87)
Median (Min, Max)	1.14 (0.55, 5.38)
Missing	56

Parameters	FAS (N=210)
LDL Cholesterol (mmol/L)	
N	153
Mean (SD)	3.02 (±2.44)
Median (Min, Max)	2.46 (0.74, 24.35)
Missing	57
Triglycerides (mmol/L)	
N	154
Mean (SD)	2.96 (±3.17)
Median (Min, Max)	1.72 (0.47, 21.53)
Missing	56
BLOOD GLUCOSE	
FPG (mmol/L)	
N	159
Mean (SD)	10.25 (±5.38)
Median (Min, Max)	9.8 (3.3, 23.2)
Missing	51
HBA1C (%)	
N	209
Mean (SD)	9.06 (±1.54)
Median (Min, Max)	8.8 (5.7, 17)
Missing	2
KIDNEY FUNCTION	
Serum Creatinine (mmol/L)	
N	159
Mean (SD)	0.26 (±0.37)
Median (Min, Max)	0.09 (0.04, 2.01)
Missing	51

FPG= Fasting Plasma Glucose, HbA1C= Glycated hemoglobin, HDL= High Density Lipid, LDL= Low Density Lipid, Max= Maximum, Min= Minimum, n = Number of patients, SD=Standard Deviation

6.2.3 Medication Summary

Dapagliflozin was the most commonly used SGLT2 inhibitor, while other anti-hyperglycemic medications used commonly included metformin, sitagliptin, glicazide, metformin XR and glipizide. The details of all the medications used by the study participants have been provided in the appendix 1.

6.2.4 Primary Objective:

Change in HbA1c during the 52 weeks follow-up

A significant decrease in the mean HbA1c level was noted at the 52 weeks follow up (mean difference: 1.13±0.11; p <.0001; Table 6-7).

Table 6-7. Difference in HbA1c levels between Baseline and Week 52

HBA1c (%)	Baseline	24 weeks	52 weeks	104 weeks	Mean difference	P value*
N	209	180	167	101	1.13	<.0001
Mean	9.06	7.97	7.97	7.95		
SD	1.54	2.89	2.01	2.07		
Median	8.8	7.6	7.7	7.7		
Min	5.7	5	5.2	5.5		
Max	17	12.8	12.7	13.3		

*P-value (baseline vs 52 weeks) is estimated based on t test

6.2.5 Secondary Objective:

Change in other parameters at 52 weeks

The secondary objectives included analyses of changes in terms of FPG, weight, blood pressure, lipids, serum creatinine, BMI, and waist circumference at the end of 52 weeks. Percentage of patients reaching the target of HbA1c <7.0% at the end-point and the frequency of hypoglycaemic events (major and minor) were also assessed. Table 6-8 enumerates the changes noted at the end of 52 weeks and the significance values.

Table 6-8. Difference between Baseline and Week 52 in terms of secondary variables

	Baseline	24 weeks	52 weeks	104 weeks	Mean difference	P value
FPG (mmol/L)						
N	159	139	132	79	0.58	0.5305
Mean	10.25	8.78	8.86	8.88		
SD	5.38	5.00	5.05	5.07		
Median	9.8	8	7.75	7.9		
Min	3.3	4.2	3.2	4.1		
Max	23.2	24.8	29.8	24.2		
LDL (mmol/L)						
N	153	141	140	87	-0.15	0.7338
Mean	3.02	2.64	2.62	2.49		
SD	2.44	1.52	1.34	1.32		
Median	2.46	2.45	2.54	2.37		
Min	0.74	0.67	0.33	0.61		
Max	24.35	5.77	5.43	6.49		
HDL (mmol/L)						
N	154	144	142	88	-0.18	0.4813
Mean	1.36	1.26	1.26	1.33		

SD	0.87	0.70	0.62	0.87		
Median	1.14	1.14	1.18	1.14		
Min	0.55	0.61	0.53	0.61		
Max	5.38	3.44	3.16	5.9		
Triglycerides (mmol/L)						
N	154	144	142	88	-0.05	0.9499
Mean	2.96	2.10	2.18	2.11		
SD	3.17	1.61	2.01	1.89		
Median	1.72	1.67	1.70	1.61		
Min	0.47	0.61	0.21	0.52		
Max	21.53	10.32	15.95	12.26		
Total cholesterol (mmol/L)						
N	153	144	140	88	-0.4	0.6355
Mean	5.15	4.59	4.59	4.20		
SD	3.14	2.43	2.27	1.98		
Median	4.43	4.32	4.34	3.95		
Min	1.75	2.12	2.28	1.58		
Max	15.04	10.21	13.45	10.65		
Serum creatinine (mmol/L)						
N	159	149	141	92	0.09	0.0137
Mean	0.26	0.08	0.13	0.12		
SD	0.37	0.07	0.19	0.15		
Median	0.09	0.08	0.08	0.08		
Min	0.04	0.01	0.03	0.03		
Max	2.01	0.92	1.24	0.95		
BMI (kg/m^2)						
N	151	133	126	87	0.78	<.0001*
Mean	30.23	29.72	29.85	29.03		
SD	14.46	15.11	15.35	14.79		
Median	29.25	28.49	29.34	28.24		
Min	19.35	20.27	20.50	19.33		
Max	49.80	53.44	52.58	43.67		

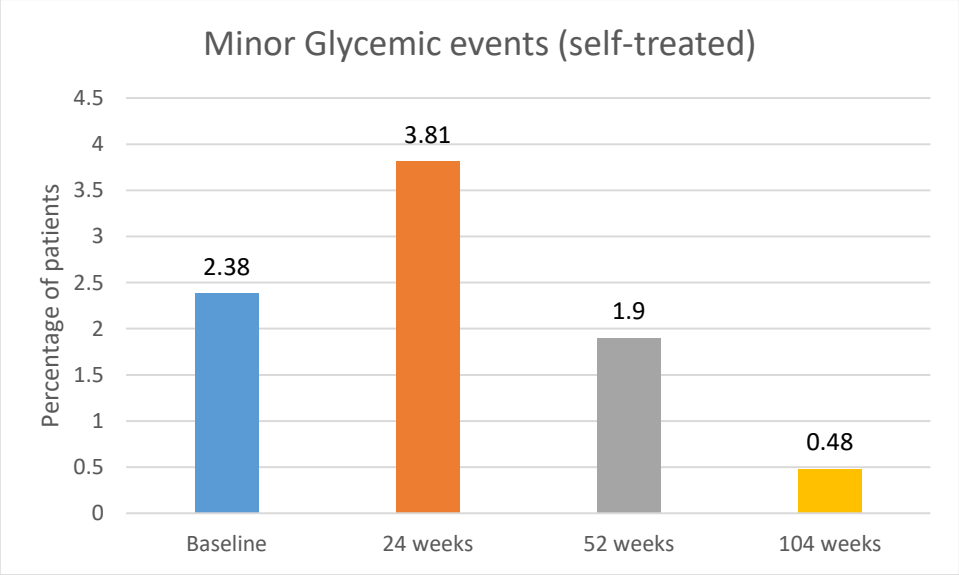
*Significant P-value; FPG= Fasting Plasma Glucose, SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, HDL= High Density Lipid, LDL= Low Density Lipid. Mean difference was calculated using formula, 52 weeks – baseline for each individual patient and mean has been taken

A significant difference in SBP, DBP, weight, BMI and waist circumference were noted at the end of week 52 (Table 6-8). Although non-significant, a reduction in other parameters including serum creatinine (0.09 mmol/L; p=0.0137) FPG (0.58 mmol/L; p =0.5305) and cholesterol levels (Table 6-8) was noted.

6.2.5.1 Glycemic events

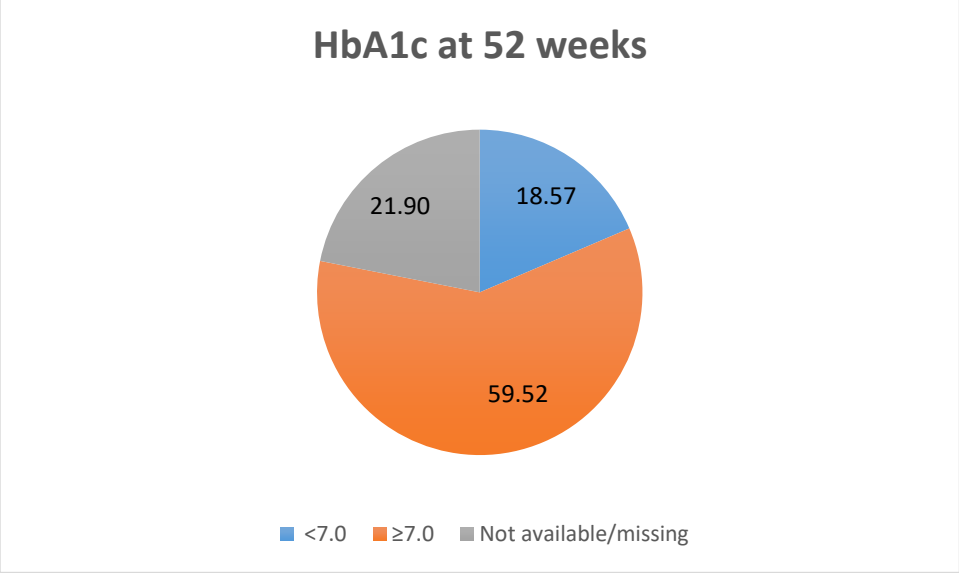
There were no major hypo glycemic events (requiring hospitalization) noted during the entire study period (Figure 2). Four minor events (self-treated) were reported at week 52.

Figure 2. Graph depicting minor hypoglycaemic events



A total of 39 (18.6%) patients reached the target of HbA1c <7.0% at 52 weeks (Figure 3).

Figure 3. HbA1c level at week 52



7. SAFETY EVALUATION

7.1 Adverse Events

A total of 99 adverse events (Figure 4, Table 7-9) including 6 serious adverse events (SAEs) were reported in 60 patients (28.6%). Among these, a definite relation to the study drug was reported in 2 cases (2.02%; Figure 5-a). The medication had to be withdrawn in 5 cases (5.05%; Figure 5-c). Medication to resolve the AE were provided in 77% of the cases and majority (88%) of the events resolved without any sequelae (Figure 5-d).

Figure 4. Adverse events

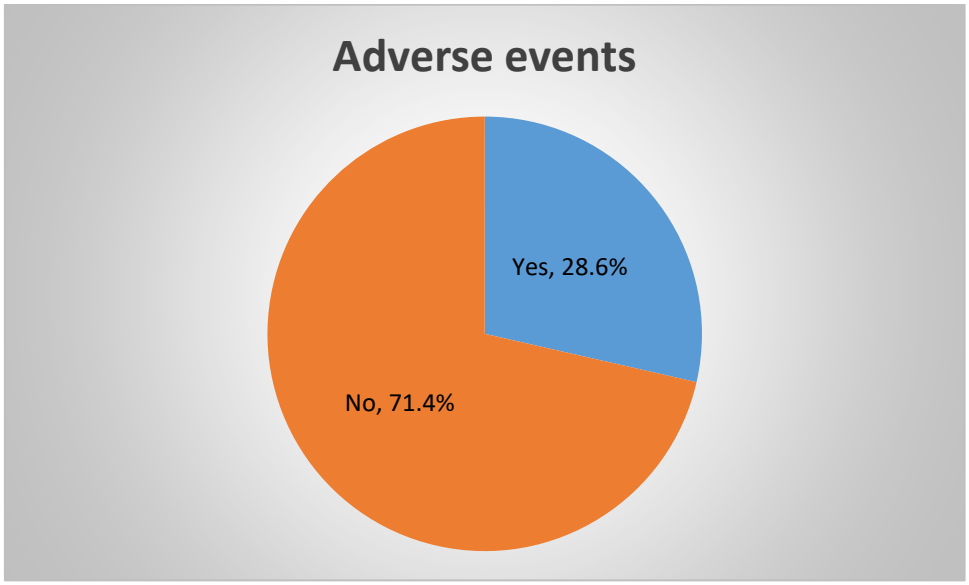


Table 7-9. Details about Adverse Events

Total number of events	99	
Adverse events	93	93.9
Serious adverse events	6	6.1

The most commonly reported adverse events included chest pain (4.8%), gasteroenteritis (2.4%), urinary tract infection (2.4%), epigastric pain (1.9%), right shoulder pain (1.9%) and shortness of breath (1.9%). Table 7-10 enumerates all the adverse events.

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8. CONCLUSION & DISCUSSION

8.1 Discussion

The current non- interventional, observational, multicentre, retrospective (existing patients on SGLT2i), and prospective study revealed several positive outcomes following management of T2DM with SGLT2 inhibitors. Earlier studies have enumerated the benefits of SGLT2i in terms of improved blood glucose levels, and reduction in blood pressure and weight (7).

A significant decrease in the HbA1c levels was noted in the current study at 52 weeks following the introduction of SGLT2i. A significant improvement in glycemic control with SGLT2i among patients with T2DM has been reported in several meta-analyses (8). It was noted that the maximum reduction in HbA1c levels occurred within a span of 6 months and was maintained until 1 year (9). This class of drug has a favourable effect in the reduction of HbA1c levels according to data available from 58 clinical trials (10). Apart from improving blood glucose levels, SGLT2 inhibitors are also known to exert numerous other benefits (7). Accordingly, significant difference in terms of SBP, DBP, weight, BMI and waist circumference were noted at the end of week 52 in the current study. Further, although non-significant, a considerable reduction in other parameters including FPG, cholesterol and serum creatinine levels was also noted. Weight reduction of up to 3 kg has been reported with the use of SGLT2 inhibitors (11). This reduction in body weight was attributed to a reduction in the body fat mass (12). Significant decrease in waist circumference as well as visceral fat has been noted in obese patients over a period of 6 months (13).

The influence of SGLT2i on blood pressure and cholesterol levels has also been well proven. Hypertension is commonly noted in individuals diagnosed with T2DM and is considered as a major risk factor for cardiovascular diseases. Reduction in blood pressure levels decreases the risk of T2DM associated macro- and microvascular complications (14). The reduction in SBP and DBP levels has been attributed to the influence of SGLT2i on osmotic diuresis and mild natriuresis (15).

Adverse events following the therapy with SGLT2i were noted in 28% of the patients with a direct relation to the drug reported in only about 2% of the cases. The most commonly reported adverse events in the current study included urinary tract infection, chest pain, shortness of breath, gastroenteritis, and epigastric pain. Majority of the adverse events resolved without any sequelae. However, there were no major hypo/hyperglycaemic events reported at week 52. Overall, the SGLT2 inhibitors are reported to be well tolerated (14). They are also considered safe when administered as monotherapy or in combination with other oral anti-diabetes agents and insulin (8)

There were a few limitations in this study. The initial sample size of the study was estimated to be 600. However due to slow recruitment and availability of alternative evidence such as CV REAL studies, it was decided to do a protocol amendment and close the study with the number patients already recruited. Further, the follow up duration was limited to 52 weeks instead of 104 weeks. Therefore, the results obtained are of exploratory nature. Nevertheless, the outcomes of the study with a limited number of study participants show promising results and are helpful in planning further research.

8.2 Conclusion

The outcomes of the current study suggest that SGLT2i are relatively effective in T2DM patients and brings about a significant decrease in HbA1c levels. Considerable reduction in weight, waist circumference, BMI, cholesterol and blood pressure levels were also noted. Although associated with a few of commonly known adverse effects, based on the widely available safety data, SGLT2i can be considered an effective option in T2DM.

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Medication prescribed	Baseline		24 Wks		52 Wks		104 Wks	
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