TIME TO NON-PERSISTENCE OF SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITORS AND ITS PROGNOSTIC FACTORS AMONG PATIENTS WITH TYPE 2 DIABETES IN UNIVERSITI MALAYA MEDICAL CENTRE

by

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LIST OF ABBREVIATIONS

ACC	American College of Cardiology
AHR	Adjusted hazard ratio
AKI	Acute kidney injury
ASCVD	Atherosclerotic cardiovascular disease
CI	Confidence interval
CKD	Chronic kidney disease
CPG	Clinical practice guidelines
CVD	Cardiovascular disease
DCA	Drug Control Authority
DKA	Diabetic ketoacidosis
DKD	Diabetic kidney disease
DPP4i	Dipeptidyl peptidase-4 inhibitors
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ESKD	End-stage kidney disease
GDMT	Guideline-directed medical therapy
GLD	Glucose-lowering drugs
GLP-1RA	Glucagon-like peptide-1 receptor agonists
HbA1c	Glycated haemoglobin
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
IHD	Ischaemic heart disease
JEPeM	*Jawatankuasa Etika Penyelidikan Manusia*
LML	Log minus log
MACE	Major adverse cardiovascular events
MAKE	Major adverse kidney events
MI	Myocardial infarction

MOH	Ministry of Health Malaysia
MPR	Medication possession ratio
MREC	Medical Research and Ethics Committee
NHMS	National Health and Morbidity Survey
NMRR	National Medical Research Registry
NPRA	National Pharmaceutical Regulatory Agency
RCT	Randomised clinical trials
RR	Risk ratio or Relative risk
SE	Standard error
SGLT2i	Sodium-glucose cotransporter-2 inhibitors
T2D	Type 2 diabetes
UMMC	Universiti Malaya Medical Centre
US	United States of America
USFDA	United States Food and Drug Administration
WHO	World Health Organization

LIST OF SYMBOLS

B	Beta coefficient
<	Less than
>	More than
≤	Less than or equal to
≥	More than or equal to
±	Plus minus
α	Type 1 error
β	Type 2 error
n	Number of sample
ml	Milliliter
min	Minute
m^2	Meter squared

MASA SEHINGGA TIADA PENERUSAN *SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITORS* DAN FAKTOR PROGNOSTIKNYA DALAM KALANGAN PESAKIT DIABETES JENIS 2 DI PUSAT PERUBATAN UNIVERSITI MALAYA

ABSTRAK

Pengenalan: *Sodium-glucose cotransporter-2 inhibitors* (SGLT2i) telah muncul sebagai rawatan perubatan baharu yang disarankan garis panduan (GDMT) untuk menguruskan sindrom kardiovaskular-buah pinggang-metabolik. Memahami corak penerusan rawatan SGLT2i boleh membantu mencegah tiada penerusan rawatan secara tidak wajar dan pada masa yang sama mengurangkan akibat negatifnya. Kajian ini bertujuan untuk menilai masa penerusan rawatan SGLT2i dan menentukan faktor prognostik untuk masa penerusan SGLT2i di kalangan orang dewasa dengan diabetes jenis 2 (T2D) di Pusat Perubatan Universiti Malaya, Kuala Lumpur, Malaysia. **Kaedah:** Kajian ini adalah kajian kohort retrospektif yang melibatkan orang dewasa berumur 18 tahun dan ke atas dengan T2D yang menerima rawatan SGLT2i di antara Januari 2016 dan Disember 2021. Hasil kajian adalah masa sehingga tiada penerusan SGLT2i, ditakrifkan sebagai masa sehingga jurang 90 hari pertama selepas tarikh anggaran bekalan farmasi tamat. Kaplan-Meier digunakan untuk menganggarkan masa median penerusan rawatan SGLT2i, analisis jadual hayat digunakan untuk mendapatkan kadar penerusan rawatan dan regresi *Cox Proportional Hazard* digunakan untuk mengenal pasti faktor prognostik untuk penerusan rawatan. **Keputusan:** Kajian ini melibatkan 602 orang dewasa dengan T2D, dengan majoriti adalah lelaki (52.0%). Purata umur pesakit ialah 60.1 tahun (sisihan piawai (SP) = 10.7). Masa median penerusan rawatan SGLT2i ialah 40.5 bulan (95% selang keyakinan (SK) 34.6, 54.0). Kadar penerusan rawatan menurun daripada 94.5% pada bulan keenam, kepada 78.0% pada tahun pertama, dan 62.7% pada

tahun kedua rawatan. Pesakit dengan anggaran kadar penurasan glomerular (eGFR) kurang daripada 60 ml/min/1.73m^2 (nisbah bahaya terlaras (NBT) 1.57, 95% SK 1.20, 2.04; p = 0.001) didapati mempunyai risiko yang lebih tinggi untuk tiada penerusan SGLT2i, berbanding mereka yang mempunyai eGFR ≥60 ml/min /1.73m^2. Penggunaan DPP4i mempunyai NBT 0.75, 95% SK 0.57, 0.98; p = 0.042 untuk tiada penerusan SGLT2i. **Kesimpulan:** Separuh daripada pesakit tiada penerusan rawatan SGLT2i dalam tempoh 3.5 tahun. Garis dasar eGFR <60 ml/min/1.73m^2 dan tiada penggunaan DPP4i adalah faktor prognostik yang penting untuk tiada penerusan rawatan SGLT2i. Kajian ini memberikan informasi berharga berkaitan masa sehingga tiada penerusan SGLT2i dalam kalangan orang dewasa dengan T2D dan faktor yang terlibat untuk memudahkan pengurusan diabetes yang lebih khusus dengan tujuan untuk mengoptimumkan hasil kesihatan.

Kata kunci: tiada penerusan SGLT2i, penerusan SGLT2i, penerusan rawatan

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ABSTRACT

Introduction: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have emerged as a new guideline-directed medical therapy (GDMT) for managing cardiovascular-kidney-metabolic (CKM) syndrome. Understanding the pattern of SGLT2i treatment persistence can help prevent unwarranted non-persistence of this GDMT and simultaneously, develop interventions to mitigate its negative consequences. This study aimed to evaluate the treatment persistence time on SGLT2i and to identify the prognostic factors for SGLT2i persistence time among adults with type 2 diabetes (T2D) at the Universiti Malaya Medical Centre, Kuala Lumpur, Malaysia. **Methods:** This was a retrospective cohort study involving adults aged 18 years and above with T2D who were initiated with SGLT2i between January 2016 and December 2021. The study outcome was time to SGLT2i non-persistence, defined as the time to first 90-day gap after the estimated end date of pharmacy supply. Kaplan-Meier estimate was used for median SGLT2i persistence time, life table analysis was used for obtaining persistence rates and Cox Proportional Hazard regression was used to identify the prognostic factors for the time to treatment persistence. **Results:** This study involved 602 adults with T2D, with the majority being male (52.0%). The mean age of patients was 60.1 years (standard deviation (SD) = 10.7). The median treatment persistence time was 40.5 months (95% confidence interval (CI): 34.6, 54.0). Treatment persistence rates reduced from 94.5% at 6 months to 78.0% at 1 year, and 62.7% at 2 years. Patients with baseline estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 had an adjusted hazard ratio (AHR) of 1.57 (95% CI

1.20, 2.04; p = 0.001) for non-persistence of SGLT2i, compared to those with eGFR ≥60 ml/min/1.73m^2. The use of DPP4i had an AHR of 0.75 (95% CI 0.57, 0.98; p = 0.042) for non-persistence of SGLT2i. **Conclusions:** Half of the patients discontinued SGLT2i within 3.5 years. Those with baseline eGFR <60 ml/min/1.73m^2 and without concomitant DPP4i use were significantly associated with SGLT2i non-persistence. This study provides valuable insights into the time to SGLT2i non-persistence in adults with T2D and the underlying factors to facilitate more personalised diabetes management to optimise health outcomes.

Key words: SGLT2i non-persistence, SGLT2i persistence, treatment persistence

CHAPTER 1:

INTRODUCTION

1.1 Background of the Study

Type 2 diabetes (T2D) is a global health crisis due to its increasing prevalence (World Health Organization (WHO), 2023), aside from the associated macrovascular and microvascular complications and mortality (Cavender et al., 2015). About 422 million people in low- and middle-income countries are affected. Additionally, diabetes is directly accountable for 1.5 million deaths per year. The prevalence and number of diabetes patients have steadily increased during the last few decades (WHO, 2023). Like many other countries, Malaysia has witnessed a flood in T2D cases over the past few years, where the prevalence of diabetes among adults increased from 11% in 2011 to 13% in 2015 and 18% in 2019 (Institute for Public Health, 2020).

T2D is the major cause of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) worldwide (Alicic et al., 2017) and diabetic kidney disease (DKD) has been linked to over 400,000 deaths in both developed and developing countries (Thomas, 2019). Furthermore, T2D is one of the most prominent risk factors for cardiovascular disease (CVD) (Einarson et al., 2018; Sarwar et al., 2010), and the presence of both T2D and CVD is associated with a greater death rate, despite advances in therapy (Di Angelantonio et al., 2015). According to the 2019 Diabetes Clinical Audit, 80% of patients with T2D in Malaysia have hypertension, 74% have dyslipidemia, and 84% are overweight or obese (Ministry of Health Malaysia (MOH), 2020). In 2016, 65% of new patients in Malaysia requiring dialysis had DKD, the most prevalent cause of ESKD) (Wong

& Goh, 2018).

The rising prevalence and complications of T2D have a major impact on healthcare systems, economies, and the overall well-being of individuals, affecting the lives of millions (WHO, 2023). As the demand for health care rises, it places significant financial burdens and strain on Malaysia's health system. In 2017, the annual direct healthcare costs associated with diabetes in Malaysia were 227% higher than for cancer and 11% higher than for cardiovascular disease (MOH, 2022).

Effectively managing T2D is essential to avoid complications, improve the quality of life for affected individuals, and lessen the societal and economic consequences of this widespread issue. The treatment of T2D requires a holistic approach that integrates lifestyle modifications and medications. Management of T2D is difficult because of the disease's complicated nature, its slow progression, and the challenges individuals encounter with adhering to treatment, tolerating it, and expressing preferences.

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have shown to be a promising class of glucose-lowering drugs (GLD). In addition to improving glycaemic control (Pinto et al., 2015), they also offer cardiovascular and renal advantages (Neal et al., 2017; Perkovic et al., 2019; Wiviott et al., 2019; Zinman et al., 2015). Based on these proven findings, the MOH commands that SGLT2i be added as part of the glucose-lowering regimen in patients with T2D with atherosclerotic cardiovascular disease (ASCVD), heart failure and DKD (MOH, 2020). The 2021 American College of Cardiology (ACC) Expert Consensus advises adding SGLT2i to the

treatment regimen of individuals with heart failure with reduced ejection fraction (HFrEF) as guideline-directed medical therapy (GDMT) along with other recommended medications (Maddox et al., 2021).

Following these improvements, the use of SGLT2i has expanded worldwide, including in Malaysia. In the United States, the number of patients on SGLT2i increased more than five-fold between 2014 and 2015 (Raval and Vyas, 2018). In Malaysia, the use of SGLT2i has increased by 109.6% after the availability of empagliflozin and canagliflozin in 2016 (Pharmaceutical Services Programme, 2020). The use of SGLT2i continued to increase by 77.5% in the following year, with a four-fold rise in the public sector and a 74.2% increase in the private sector (Pharmaceutical Services Programme, 2023). Universiti Malaya Medical Centre (UMMC) was one of the earliest and largest institutions to include SGLT2i in their management of T2D in 2015, compared to MOH facilities where the use of SGLT2i remains limited.

Despite the groundbreaking evidence of SGLT2i benefits in clinical trials, real-world data has proved that maintaining long-term adherence and persistence with SGLT2i is difficult. Research indicates that patients on SGLT2i have greater non-persistence rates than other GLDs, such as dipeptidyl peptidase-4 inhibitors (DPP4i) and glucagon-like peptide-1 receptor agonists (GLP-1RA). Reasons for SGLT2i non-persistence include adverse events, non-compliance, and other factors, that can affect the management of T2D, specifically inadequate blood sugar control, complications, and increased healthcare expenses.

1.2 Problem Statement

Although the use of SGLT2i continues to increase, observational studies have indicated poor persistence with this treatment. The high non-persistence rate with SGLT2i is alarming, which could impact patient outcomes and increase the risk of developing complications such as cardiovascular disease, obesity, and kidney disease.

To the best of the researcher's knowledge, there is no study conducted on the treatment non-persistence pattern of SGLT2i in Malaysian populations. Furthermore, most of the studies were conducted based on insurance databases, where reasons causing drug non-persistence are limited, especially adverse events. Due to a lack of real-world data, knowledge of the actual patterns, risks and timing of non-persistence remains limited. This limitation hinders our ability to fully understand and address medication persistence issues.

1.3 Justification of the Research

Due to the chronic nature of diabetes and the necessity for continued glycaemic management to prevent complications, it is important to analyse the non-persistence of diabetes drugs, especially in the Malaysian population, which is at high risk for diabetes-related complications. The overwhelming evidence of cardioprotective and renoprotective advantages, which leads to indication in a much larger patient population, necessitates a better understanding of the reasons for SGLT2i treatment non-persistence and preventative strategies, especially for high-risk patients.

It is important to explain this treatment's real-world persistence where, in acute illness and scheduled surgery, consensus recommendations still encourage temporarily discontinuing SGLT2i therapy. Healthcare providers can educate patients on the risk of non-persistence, provide counselling, and encourage persistent use of these medications for cardiovascular and renal advantages to improve patient outcomes. Unwarranted SGLT2i non-persistence can be prevented by understanding the pattern of treatment non-persistence, thus, interventions to reduce its negative consequences can be developed. By identifying the factors associated with drug non-persistence, healthcare providers may improve medication persistence and indirectly reduce T2D management expenditures.

Therefore, SGLT2i non-persistence risks should be assessed. This research is expected to help physicians and health policymakers develop better T2D management strategies for patients receiving SGLT2i.

1.4 Research Question(s)

1. What is the median persistence time on SGLT2i among patients with T2D in the UMMC?
2. What are the six-month, one-year and two-year SGLT2i persistence rates among patients with T2D in the UMMC?
3. What are the prognostic factors for SGLT2i persistence time among patients with T2D in the UMMC?

1.5 Research Objective

1.5.1 General Objective:

To evaluate the time to non-persistence of SGLT2i and to identify the prognostic factors for SGLT2i persistence time among patients with T2D in the UMMC.

1.5.2 Specific Objective:

1. To determine the median persistence time on SGLT2i among patients with T2D in the UMMC.
2. To determine the six-month, one-year and two-year SGLT2i persistence rates among patients with T2D in the UMMC.
3. To identify the prognostic factors for SGLT2i persistence time among patients with T2D in the UMMC.

1.6 Research Hypothesis

1. The SGLT2i persistence rate among patients with T2D in the UMMC is decreasing over time.
2. The significant prognostic factors for SGLT2i persistence time among patients with T2D in UMMC are patient-related, clinical-related and medication-related.

CHAPTER 2:

LITERATURE REVIEW

2.1 Methods of Literature Search

Literature was searched using search engines such as Google Scholar, ScienceDirect and PubMed for articles discussing the treatment discontinuation of SGLT2i, its prognostic factors and safety-related information. The literature search was done using phrase searching, citation searching and Boolean operators. Combinations of the following keywords were used: *prognostic factors, discontinuation, treatment persistence, non-persistence, sodium-glucose cotransporter-2 inhibitors, cardiovascular safety, renal safety and adverse events leading to discontinuation.* All the articles were imported into Mendeley Reference Manager.

2.2 Type 2 Diabetes (T2D)

Progressive declines in beta-cell function and insulin resistance in muscle and adipose tissue characterise T2D. The insulin-resistant state results in increased hepatic glucose output and decreased glucose utilisation by various organs, which contributes to hyperglycaemia during fasting and between meals. Inadequate intestinal incretin secretion leads to impaired meal-related insulin secretion and glucagon suppression, which contributes to postprandial hyperglycaemia. In addition, excessive renal tubular glucose reabsorption contributes to hyperglycaemia (American Diabetes Association, 2010). Hyperglycaemia may be caused by physiological defects in insulin action, insulin secretion, or both. Chronic hyperglycaemia is associated with long-term injury,

dysfunction, and failure of multiple organs, particularly the eyes (diabetic retinopathy), kidneys (diabetic nephropathy), nerves (diabetic neuropathy), heart, and blood vessels (American Diabetes Association, 2010).

2.2.1 The Goals and Challenges of T2D Management

T2D is a chronic and complicated metabolic disorder that keeps challenging the healthcare system worldwide. The increasing prevalence of T2D creates a substantial cost for individuals, healthcare professionals, and society in general. The management of T2D is complex, requiring a complicated approach that includes lifestyle modifications and pharmacological interventions. In general, the effective management of T2D is primarily focused on lowering acute and chronic complications associated with diabetes to improve quality of life, prevent premature death, and mitigate the societal and economic consequences of this epidemic. This can be accomplished specifically by targeting plasma glucose, blood pressure, lipids, and body weight control simultaneously (MOH, 2020). The management of T2D involves various factors, which include ongoing patient education, dietary changes, regular physical activity, and the administration of multiple medications. Furthermore, the variable disease progression, together with factors such as treatment adherence, tolerability, and patient preferences, can complicate the selection of an appropriate treatment regimen.

The Asian population presents unique challenges in the management of T2D. Several different characteristics set Asian patients apart from Caucasian patients (Lim et al., 2017). These include a higher risk of getting diabetes at a lower body mass index, more central obesity and

visceral adiposity, which increase resistance to insulin. Additionally, there is a decrease in beta cell function, which worsens issues with insulin secretion (Kalra et al., 2017; Kodama et al., 2013; Lim et al., 2017). Diabetes is diagnosed in as many as one in five Asians before the age of 40 (Yeung et al., 2014). With longer diabetes duration, these patients have a greater chance of developing diabetes complications, as well as poorer glycaemic control compared to patients with late-onset diabetes (Ma & Chan, 2013). These phenotypes position Asian patients at a significantly higher risk for diabetes-related complications at a younger age (Lim et al., 2017).

In Malaysia, of those with known diabetes, 25.7% were treated with insulin, 85.6% with oral GLDs, and 88.0% had dietary guidance given to them (Institute for Public Health, 2020). Based on the 2019 Diabetes Clinical Audit (National Diabetes Registry), the most prescribed oral GLDs among individuals with T2D were metformin and sulfonylureas (83% and 44%, respectively) (MOH, 2020). Despite being the first-line treatment for diabetes, metformin utilisation has decreased by 9.5% from 2015 to 2016, as well as a reduction in usage of sulfonylurea by 9.6% (Pharmaceutical Services Programme, 2020), which may be due to the introduction of a newer class of GLDs, such as DPP4i, SGLT2i and GLP-1RA. These newer classes of medications have demonstrated the potential to transform the way T2D is approached, offering advantages such as improved glycaemic control, weight loss, and cardiovascular benefits (MOH, 2020).

In light of the high and rising co-morbidities and complications among patients with T2D in Malaysia, a new paradigm shift in pharmacological therapy choice is anticipated. This new approach in T2D therapy is supplemented by major cardiovascular outcome trials supporting the

benefits of more unique classes of GLDs, specifically SGLT2i and GLP-1RA (MOH, 2020). Thus, recent guidelines, including the Malaysian Clinical Practice Guidelines (CPG), recommend these drugs as the preferred choice of therapy for individuals with CVD or at high risk of developing it.

2.3 Sodium-Glucose Co-Transporter 2 Inhibitors

One of the innovative therapeutic classes that have shown promise in T2D management is SGLT2i. In contrast to other types of GLDs, SGLT2i reduces blood glucose by an insulin-independent mechanism that targets the kidney to encourage urine glucose excretion (White, 2015). The glucose co-transporter protein SGLT2 is important in mediating glucose reabsorption in the proximal tubule of the kidney (Bakris et al., 2009). In patients with T2D, inhibition of SGLT2 decreases the renal threshold for glucose, causing an increase in urine glucose excretion, and lowering blood glucose levels. Increased urine glucose excretion also causes a net calorie loss and a modest osmotic diuresis, which may lower blood pressure and body weight (Defronzo et al., 2012; Rosenstock et al., 2012; Wilding, 2014).

Canagliflozin, dapagliflozin, empagliflozin and luseogliflozin are among the SGLT2i licensed for treating T2D worldwide. Dapagliflozin was the first SGLT2i to receive approval in Malaysia from the Drug Control Authority (DCA), MOH in January 2014 (National Pharmaceutical Regulatory Agency (NPRA), 2014), then empagliflozin in December 2015 (NPRA, 2015b), canagliflozin in April 2016 (NPRA, 2016), and luseogliflozin in September 2018 (NPRA, 2023). Some of the SGLT2i members have also been approved as fixed-dose combinations with other glycaemic-lowering agents such as metformin, saxagliptin and linagliptin.

Initially, all SGLT2i members were approved for the treatment of T2D. Later, it was discovered that these medications not only improved glycaemic control but also had additional cardiovascular and kidney benefits (Neal et al., 2017; Perkovic et al., 2019; Wiviott et al., 2019; Zinman et al., 2015). As a result, these drugs are now approved for use in other indications such as heart failure and CKD (Forxiga®, 2023; Jardiance®, 2023; Invokana®, 2022). Table 2.1 lists Malaysia's approved indications for each SGLT2i member:

Table 2.1: List of SGLT2i and their approved indications in Malaysia

SGLT2i Members	Approved Indications
Dapagliflozin	**Type 2 diabetes mellitus** Forxiga* is indicated in adults aged 18 years and older with type 2 diabetes mellitus as: Monotherapy When diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance. Add-on combination therapy In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control. Initial Combination Forxiga is indicated for use as initial combination therapy with metformin, as an adjunct to diet and exercise, to improve glycaemic control in patients with type 2 diabetes mellitus when diet and exercise have failed to provide adequate glycaemic control and there are poor prospects for response to metformin monotherapy (for example, high initial HbA1c levels). To reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD) or multiple cardiovascular (CV) risk factors.

Table 2.1: *continue*

	Heart failure Forxiga is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction. **Chronic kidney disease** Forxiga is indicated in adults for the treatment of chronic kidney disease. (Forxiga Malaysia Package Insert, 2023)
Empagliflozin	**Type 2 diabetes mellitus** **Glycaemic control** Jardiance* is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as: Monotherapy When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance. Add-on combination therapy In combination with other glucose–lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control. **Prevention of cardiovascular death** Jardiance is indicated in patients with type 2 diabetes mellitus and established cardiovascular disease to reduce the risk of cardiovascular death. To prevent cardiovascular deaths, Jardiance should be used in conjunction with other measures to reduce cardiovascular risk in line with the current standard of care. **Heart failure** Jardiance is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV). (Jardiance Malaysia Package Insert, 2023)

Table 2.1: *continue*

Canaglflozin	<u>Monotherapy</u> INVOKANA* (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus for whom metformin is inappropriate due to contraindications or intolerance. <u>Combination with Metformin and either a Sulfonylurea or Pioglitazone</u> INVOKANA is indicated in combination with metformin and either a sulfonylurea or pioglitazone in adult patients with type 2 diabetes mellitus to improve glycemic control when diet, exercise, and dual therapy (with metformin plus either a sulfonylurea or pioglitazone) do not provide adequate glycemic control. <u>Combination with Insulin</u> INVOKANA is indicated as add-on combination therapy with insulin (with or without metformin) in adult patients with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control when diet and exercise, and therapy with insulin (with or without metformin) do not provide adequate glycemic control. <u>Add-On Combination in Patients with Established Cardiovascular Disease</u> INVOKANA is indicated as an adjunct to diet, exercise, and standard of care therapy to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adult with type 2 diabetes mellitus and established cardiovascular disease (CVD). <u>Patients with Diabetic Nephropathy</u> INVOKANA is indicated as an adjunct to diet, exercise, and standard ofcare therapy to reduce the risk of end-stage kidney disease, doubling of serum creatinine, and cardiovascular (CV) death in adult patients with type 2 diabetes mellitus and diabetic nephropathy with albuminuria (>33.9 mg/mmol). (Invokana Malaysia Package Insert, 2022)

Table 2.1: *continue*

Luseogliflozin	Lusefi* is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as: <u>Monotherapy</u> When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance. <u>Add-on combination therapy</u> In combination with glucose-lowering medicinal products including insulin preparations in adult patients with type 2 diabetes mellitus to improve glycaemic control when diet and exercise plus monotherapy does not provide adequate glycaemic control. (Lusefi Malaysia Package Insert, 2021)

* Forxiga, Jardiance, Invokana & Lusefi are the approved brand names for dapagliflozin, empagliflozin, canagliflozin & luseogliflozin, respectively, in Malaysia.

The positive results obtained from ground breaking clinical trials have resulted in a global rise in the utilisation of SGLT2i. Between 2014 and 2015, there was a more than five-fold increase in the percentage of patients on SGLT2i medication in the United States, rising from 0.8% to 4.4% (Raval & Vyas, 2018). The utilisation of SGLT2i in Malaysia has had a significant surge of 109.6% after the introduction of empagliflozin and canagliflozin in 2016, as reported by the Pharmaceutical Services Programme (2020). The introduction of SGLT2i has broadened the selection of GLDs that can be used for T2D.

2.3.1 Benefits of SGLT2i

SGLT2i has been proven to have additional benefits for weight loss and reduction of both systolic and diastolic blood pressure, on top of the reduction of HbA1c (Pinto et al., 2015), with a low risk of hypoglycaemia (Fitchett et al., 2016). It has also been shown to significantly reduce major adverse cardiovascular events (MACE) endpoints in T2D with ASCVD (Zinman et al., 2015; Neal et al., 2017) and reduce hospitalisation for heart failure (Zinman et al., 2015; Neal et al., 2017; Wiviott et al., 2019; Cannon et al., 2020). One trial, DAPAHF, demonstrated a lower risk of cardiovascular death or heart failure with dapagliflozin compared to a placebo, regardless of diabetes status (McMurray et al., 2019). Aside from the cardiovascular benefits, this class of drugs is effective in reducing renal endpoints and related mortality among patients with T2D at high cardiorenal risk (Perkovic et al., 2019, Lim et al., 2023). The renoprotective effect of SGLT2i has now been extended to non-diabetic CKD (Heerspink et al., 2020), indicating that the renoprotective effect of SGLT2i is consistent regardless of diabetes status (McMurray et al., 2019; Packer et al., 2020).

The impressive reduction in cardiovascular morbidity and mortality, as well as the progression of kidney disease in a variety of patient populations, somewhat overshadowed their function in glucose control. This resulted in modifications to CPG for treating both heart failure and DKD. Based on these proven findings, the CPG for the Management of T2D, MOH, commands that SGLT2i be added as part of the glucose-lowering regimen in patients with T2D with established ASCVD and among patients with ASCVD with pre-existing or high-risk heart failure. The CPG also recommends SGLT2i be used in patients with albuminuria and DKD down

to estimated glomerular filtration rate (eGFR) 30ml/min/1.73m^2 to reduce DKD progression (MOH, 2020). Following these advancements, it is expected that the use of SGLT2i will expand further in Malaysia, especially among cardiologists and nephrologists alongside endocrinologists.

2.3.2 Safety of SGLT2i

Although the groundbreaking studies demonstrated that SGLT2i significantly lowers the risk of cardiovascular morbidity and mortality and slows the progression of kidney disease, regulatory agencies such as the United States Food and Drug Administration (USFDA), the European Medicines Agency (EMA), and even the NPRA have issued safety warnings for several SGLT2i-related adverse events. Based mostly on case report data, they include acute kidney injury (AKI), diabetic ketoacidosis (DKA), genital infections, bone fractures, and lower limb amputations (EMA, 2016; NPRA, 2015a & 2022; USFDA, 2015, 2016, 2017, 2018 & 2022). Due to its unique mode of action (Idris & Donnelly, 2009), SGLT2i may cause additional adverse effects not seen with other GLDs, such as infections and genital tract symptoms, dehydration, and hypovolemia (Lupsa & Inzucchi, 2018; Neuen et al., 2022). The much less common adverse events linked to SGLT2i are pyelonephritis and Fournier's gangrene (Bonora et al., 2018).

According to pharmacovigilance investigations comparing AKI events in various SGLT2i, the proportion of AKI reports among cases with SGLT2i was significantly higher than the proportion of AKI reports among cases with T2D who did not receive SGLT2i (reporting odds ratio (ROR) 1.68; 95% CI 1.57, 1.80; $p < 0.001$) (Perlman et al., 2017). This result validated the data from regulatory agencies. Among the SGLT2i, canagliflozin had the strongest association

with AKI (Chen et al., 2022; Perlman et al., 2017).

A meta-analysis of randomised clinical trials (RCTs) found that SGLT2i was significantly protective against AKI (risk ratio (RR) 0.59; 95% CI 0.39, 0.89; I^2 = 0.0%), DKA (RR 0.66; 95% CI 0.30; 1.45, I^2 = 0.0%) and bone fracture (RR 0.87; 95% CI 0.69, 1.09; I^2 = 1.3%). When all events were compared between different SGLT2i members, the results were identical (Donnan et al., 2019). This meta-analysis included only patients with T2D. When other chronic diseases were considered, however, different outcomes were identified. Another meta-analysis of eight RCTs was conducted to evaluate the safety of SGLT2i in patients with various chronic diseases, including T2D, chronic heart failure and CKD. SGLT2i was found to significantly increase the risk of DKA (RR 2.57; 95% CI 1.54, 4.31; I^2 = 2.9%). The study also revealed an increase in genital infection, volume depletion, fracture, amputation, and urinary tract infection risks. Nonetheless, similar to the earlier meta-analysis, this study demonstrated that SGLT2i significantly reduced the risk of AKI when compared to placebo (RR 0.75; 95% CI 0.66, 0.85; I^2 = 0%). These effects persisted across four SGLT2i (dapagliflozin, empagliflozin, ertugliflozin, and canagliflozin) and the three chronic diseases (Qiu et al., 2021).

Malaysia's pharmaceutical regulatory agency, NPRA, has included specific precautions in the safety profile of SGLT2i, including adverse events, such as DKA, genital infections, and lower limb amputation, to notify healthcare providers and patients of the risks. Despite that some of the events are rare, they can lead to serious complications, highlighting the importance of strict monitoring of patients, especially in high-risk populations. The CPG for the Management of T2D, MOH, recommended that SGLT2i be avoided in patients with severe CKD and an eGFR of less

than 30 ml/min/1.73m^2 who are initiating dialysis (MOH, 2020). In cases of surgeries, the CPG also advised SGLT2i to be temporarily withheld (at least three days prior) to lessen the risk of developing ketoacidosis after surgery (USFDA, 2022). Healthcare professionals are advised by the NPRA to discontinue SGLT2i if ketoacidosis is suspected or confirmed. This is on top of the thought that SGLT2i should be discontinued when patients experience problems with their lower limbs because of the increased risk of amputations associated with the medication. Finally, although other genital diseases were not mentioned, suspicion of Fournier's gangrene was also cited as a reason to discontinue SGLT2i (Forxiga®, 2023; Jardiance®, 2023; Invokana®, 2022).

2.4 Persistence to SGLT2i

Medication persistence and compliance have two different definitions. Medication compliance, also known as adherence, is the extent to which a patient complies with the healthcare provider's instructions regarding the dosage and frequency of their daily medications. "The extent to which a patient acts following the prescribed interval, and dose of a dosing regimen" is one definition for it. While continuing treatment for the whole recommended duration is referred to as medication persistence (or treatment continuation). It can be defined as "the amount of time from the start of therapy to its end" (Cramer et al., 2008). Duration serves as a measure of persistence, whereas the proportion of prescribed doses taken within a given period serves as a measure of medication adherence. Non-persistence of therapy (or discontinuation) is typically a healthcare provider-approved modification of the treatment regimen prompted by a change in clinical circumstances (Wu et al., 2021). Treatment discontinuation and medication possession ratio (MPR) were the most often reported adherence quantification metrics in studies measuring

adherence to oral GLDs (Holdt-Caspersen et al., 2024).

In general, adverse effects, as well as other factors such as demographic characteristics, administration route, clinical factors and costs, affect drug adherence and persistence, which may then lead to negative clinical and public health implications (Rea et al., 2021). In T2D, the complexity of administration, perception of efficacy, and adverse events are potential factors that influence therapy discontinuation (Moura et al., 2018). Reduced clinical and economic outcomes, such as poor HbA1c control, high hospitalisation rates, mortality rates, and healthcare costs, have been associated with non-persistence with GLDs (Buysman et al., 2015; Cai et al., 2016; Currie et al., 2012; Feldman et al., 2014; McAdam-Marx et al., 2015). However, treatment discontinuation may not necessarily indicate a negative outcome; it may be related to a positive reason, such as the achievement of glycaemic control, weight loss, or the initiation of other diabetes medications (Wu et al., 2021).

Studies on the non-persistence of SGLT2i that are currently accessible have varied follow-up lengths, spanning from three months to five years, and different data sources and measures to identify medication non-persistence. A small number of these studies, however, concentrated on identifying predictors of discontinuation after treatment initiation (Cai et al., 2016; Diels & Neslusan, 2015; McGovern et al., 2018; Malik et al., 2023). Others employed a comparative design approach to compare the durability of SGLT2i to other drug classes (Bell et al., 2017; Coleman et al., 2019; Jermendy et al., 2018; Singhal et al., 2019; Ofori-Asenso et al., 2021).

A Danish real-world study was conducted to assess the five-year risk of discontinuing SGLT2i therapy in all first-time users of SGLT2i from 2013 to 2021. This study defined the non-persistence of therapy as the first event of a failure of medication supply for at least 90 days. The cumulative incidence of non-persistence of therapy for SGLT2i was used and it was found that the absolute five-year risk was 56% (95% CI 55, 57)]. A significant portion of the individuals who discontinued therapy had recently been hospitalised, which may indicate that they may have fallen out of therapy as a result of the hospitalisation. The non-persistence rates discovered in this study were lower than those reported in previous small, inconsistent observational studies, but consistent with the findings from clinical trials (Malik et al., 2023).

A study conducted using the Hungarian central database discovered that the risk of discontinuation over 24 months was 6.6% higher for SGLT2i compared to DPP4i (Jermendy et al., 2018). Nonetheless, when comparing individual members, only 29.8% of canagliflozin patients discontinued, whereas 41.5% of sitagliptin (DPP4i) patients did the same ($p < 0.001$) over 9 months. Canagliflozin patients also had a longer average days-persistence on index medication of 152 days, compared to 139 days for sitagliptin patients ($p < 0.001$) (Thayer et al., 2017). Another study conducted in the Japanese population found that SGLT2i was associated with better treatment persistence compared to DPP4i in patients with T2D (Kashiwagi et al., 2023).

When comparing once-weekly GLP-1RA administration to daily SGLT2i administration, GLP-1RA administration resulted in better persistence. GLP-1RA users had a lower risk of discontinuing drug treatment as compared to SGLT2i users (RR 0.85; 95% CI 0.75, 0.97) (Rea et al., 2021). Conversely, another retrospective cohort study discovered that the risk of

discontinuation was lower in the canagliflozin cohort than in the GLP-1RA cohort (HR 0.78; 95% CI 0.70, 0.88; $p < 0.001$) (Singhal et al., 2019). Another study also discovered that, compared to patients using GLP-1RA, those taking canagliflozin had a lower discontinuation rate (HR 0.57; 95% CI 0.45, 0.72; $p < 0.001$) (Coleman et al., 2019).

When SGLT2i members were compared individually, patients taking canagliflozin 300 mg took the longest to discontinue the medication, followed by those on canagliflozin 100 mg, those on dapagliflozin 5 mg, those on DPP4i, and lastly those on GLP-1RA. The time to discontinuation among the index therapies was significant ($p < 0.001$) (Cai et al., 2017). In another study, empagliflozin users were significantly more persistent than dapagliflozin users (HR 1.14; 95% CI 1.06, 1.22; $p<0.01$) (Ofori-Asenso et al., 2021). The persistence rates of canagliflozin and empagliflozin have not been explicitly compared in any research. The assessment of different SGLT2i members could explain the inconsistency of findings between these studies. There are also differences in the definition of persistence used in these studies, with acceptable gaps (grace periods) ranging from 60 to 180 days.

In high-risk patients with heart failure (HF), 12% of patients discontinued SGLT2i following hospital discharge. The most frequent reasons for discontinuation were bacterial infection (32%) and modification of treatment for CVD (21%). Patients who discontinued SGLT2i experienced more recurrence of HF or CV mortality over the 1-year therapeutic period than patients who continued the treatment ($p = 0.020$). Importantly, in this study, the prevalence of diabetes was no longer a predictor of SGLT2i discontinuation. The rate of SGLT2i discontinuation among participants with and without diabetes is not significantly different (Nakagaito et al., 2023).

It was shown that almost half of the study group (47.2%) discontinued SGLT2i, with 20.2% of these discontinuations being linked to an adverse event. This was in another high-risk cohort of patients with T2D and CKD. Increased creatinine levels (8%) and vaginal or urinary side effects (5.6%) were the most common reasons for discontinuation (Choi et al., 2021). Similar outcomes were seen in another trial involving patients with CKD, where 55% of the SGLT2i initiators discontinued their therapy over the 5-year follow-up period and were largely related with the development of possible SGLT2i adverse events. (Kovesdy et al., 2022).

From the perspective of clinical trials, adverse events leading to discontinuation did not differ significantly between the canagliflozin and placebo groups (35.5 vs. 32.8 events per 1000 patient-years; HR 1.13; 95% CI 0.99, 1.28; p = 0.07) (Neal et al., 2017). Four others large RCTs have reported lower discontinuation rates ranging from 10.5% to 23.2% in HF patients taking SGLT2i (Anker et al., 2021; McMurray et al., 2019; Packer et al., 2020; Solomon et al., 2022). In other RCTs, the rates of adverse events leading to non-persistence of SGLT2i were also lower (8.5% and 3.0%) (Bhatt et al., 2021; Voors et al., 2022). In these clinical trials, the non-persistence rates were lower than those reported in real-world data. Commonly, RCTs only report treatment non-persistence due to adverse events. The discrepancies between real-world data and clinical trial outcomes may further suggest that SGLT2i therapy is challenging to maintain in actual high-risk populations.

2.4.1 Six-month, One-year and Two-year SGLT2i Persistence Rates

In a retrospective cohort study using primary care data in the United Kingdom (UK), the Kaplan-Meier estimator was used to describe the persistence time among metformin users who initiated SGLT2i. The six-month, one-year and two-year persistence rates of SGLT2i were approximately 80%, 60% and 40%, respectively (Alkabbani et al., 2023). In another retrospective cohort study conducted in the UK, the proportion of people who remained persistent with SGLT2i was found to be 79.5% at 6 months after treatment initiation and decreased to 69.5% at 1 year and 54.8% at 2 years (McGovern et al., 2018). A study conducted using a primary care database in Spain assessing SGLT2i as an add-on therapy to metformin discovered similar findings, where the persistence rates at six months, one year and two years were 81.4%, 71.4% and 60.3%, respectively (Vlacho et al., 2021). Jermendy et al. (2018) discovered similar persistence rates using a central database in Hungary, where the persistence rates were 67.8% in year 1 and reduced to 56.8% in year 2.

Supporting the earlier studies, a systematic review of 11 observational studies discovered that the pooled proportions of patients' persistence towards SGLT2i, considered to be the presence of at least a 90-day gap in treatment, were 80.1% at 6 months, 61.8% at 1 year, and 45.9% at 2 years (Ofori-Asenso et al., 2021). All the mentioned studies used a gap of at least 90 days as the definition of non-persistence, whereas Jermendy et al. used a larger interval of at least 180 days.

Persistence rates differed across different SGLT2i when analysed individually. The persistence rate of canagliflozin 300 mg was 50.4% a year after treatment initiation, which was

higher than that found in the previous studies that assessed SGLT2i as a whole (Singhal et al., 2019). Cai et al. (2016) provide further comparisons between different doses of canagliflozin and other SGLT2i members. The rate of treatment persistence was lower for canagliflozin 300 mg versus canagliflozin 100 mg (64% vs. 61%, $p < 0.05$). Dapagliflozin 5 mg and dapagliflozin 10 mg were found to have poorer persistence rates than canagliflozin 100 mg (40% ($p < 0.001$), 41% ($p < 0.001$), respectively). These studies also defined treatment non-persistence as the first treatment gap of at least 90 days between two pharmacy claims.

2.4.2 Median Persistence Time on SGLT2i

Alkabbani et al. (2023) found that half of the patients remained on SGLT2i treatment (median persistence time) up to 1.51 years (95% CI 1.40, 1.60). In another study evaluating the treatment persistence of subjects who were initiated on SGLT2i as an add-on treatment to metformin, the median persistence time was approximately 11 months (Vlacho et al., 2021). Singhal et al. (2019) reported a shorter median persistence time of 6.1 months, whereas this study only evaluated canagliflozin 300 mg. A comparable finding was discovered in another trial involving patients with DKD with median persistence time on SGLT2i of 6.8 months (Kovesdy et al., 2022). The inconsistent median persistence time between these studies could be caused by the different SGLT2i members and populations under study.