# Effect Of Sodium Glucose Co-Transporter 2 Inhibitors on Weight Reduction in Overweight and Obese Population: A Review

By

Md. Tamjidur Rahman Mahin
18346051

A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelors in Pharmacy (Hons.)

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## Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

**Student's Full Name & Signature:**

**Md. Tamjidur Rahman Mahin**
18346051

# Approval

The thesis/project titled “Effect of Sodium Glucose Co-Transporter 2 Inhibitors on Weight Reduction in Overweight and Obese Population: A Review” submitted by Md. Tamjidur Rahman Mahin (18346051) of Summer 2018 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelors of Pharmacy on January 2023.

Supervisor:

_____

Dr. Eva Rahman Kabir
Professor and Dean, School of Pharmacy
Brac University

Approved By:

Program Director:

_____

Dr. Hasina Yasmin
Professor, Assistant Dean & Program Director, School of Pharmacy
Brac University

Dean:

_____

Dr. Eva Rahman Kabir
Professor and Dean, School of Pharmacy
Brac University

## Ethics Statement

I, Md. Tamjidur Rahman Mahin, hereby certify that the following criteria are fulfilled for the manuscript ‘Effect of Sodium Glucose Co-Transporter 2 Inhibitors on Weight Reduction in Overweight and Obese Population: A Review’.

1. This material is my own original material of review that has never been published beforehand.
2. The study does not include any animal or human trial.
3. All of the sources those are utilized are correctly credited (correct citation) along with a proper and justified reference.

## Abstract

Obesity is a global health concern and a large percentage of world is affected by it. Lifestyle changes are necessary and several therapy options are available to address it. Sodium glucose cotransporter 2 (SGLT-2) inhibitors show promising results in weight reduction. Although SGLT-2 inhibitors are approved by FDA for treating type 2 diabetes, recent trials have shown their effectiveness in weight loss. In the current study, the co-administration of 300 mg Canagliflozin and 15 mg phentermine has been found to have the highest efficacy, followed by 150 mg Licogliflozin once a day (q.d) and 25 mg Licogliflozin twice a day (b.i.d) which is moderately effective, and lastly 100 mg Canagliflozin once daily (q.d), which is has the lowest efficacy. Based on adverse effects like genital mycotic infection and urinary tract infections, Canagliflozin can be considered as a safe drug. Further clinical trials and post marketing data are required to confirm this finding.



**Keywords:** SGLT-2 inhibitors; obese; overweight; weight reduction; anti-obesity drugs, non-diabetic

# Dedication

*Dedicated to my treasured parents and respected supervisor*

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## List of Acronyms

| | |
|---|---|
| SGLT-1 | Sodium Glucose Cotransporter 1 |
| SGLT-2 | Sodium Glucose Cotransporter 2 |
| UGE | Urinary Glucose Excretion |
| T2D | Type 2 Diabetes |
| $C_{max}$ | Maximum Plasma Concentration |
| AUC | Area Under the Curve |
| $T_{max}$ | Time to Reach $C_{max}$ |
| q.d. | Once a day |
| b.i.d. | Twice a day |
| PBO | Placebo |
| CANA | Canagliflozin |
| PHEN | Phentermine |
| CANA/PHEN | Co-administration of Canagliflozin and Phentermine |
| BMI | Body Mass Index |
| UTI | Urinary Tract Infection |
| GI | Gastrointestinal |
| RTG | Renal Threshold for Glucose |
| FDA | Food and Drug Administration |

# Chapter 1

# Introduction

Over the decades obesity has transformed into a massive worldwide health concern. An individual can be classified as obese if their body mass index (BMI) is greater than 30 $kg/m^2$ (Pi-Sunyer, 2002). Estimations made by the World Health Organization (WHO) predict that by 2025, one out of five adults globally will be obese (Mohammed et al., 2018). Statistics show that globally obesity has nearly doubled since 1980. Statistics from 2014 show that around 1.9 billion adults of 18 years were overweight and more than 600 million of them were obese (Mohammed et al., 2018). Furthermore, statistics from 2016 show that 1.9 billion adults were obese or overweight (Pereira & Eriksson, 2019). Among these, 650 million were classified obese by WHO (Pereira & Eriksson, 2019). Obesity and overweight are tightly correlated and lead to significant risks such as osteoarthritis, strokes, hypertension, dyslipidemia, stroke, cancer just to name a few (Pi-Sunyer, 2002). There are several weight loss approaches which include medications, lifestyle changes and diet plans. One of the most effective methods which can be utilized to fight obesity is a change in lifestyle, which primarily involves cutting on the caloric intake along with an increase in physical exercise. But majority of obese or overweight individuals are reluctant to change their lifestyles to obtain their required bodyweight. To address this issue, anti-obesity drugs can be used to facilitate weight loss. However, with certain individuals the adverse effects of these drugs, especially appetite suppressive drugs are a major concern.

Among the various drugs which cause weight loss, sodium glucose cotransporter 2 inhibitors show promising results. SGLT-2 inhibitors belong to the oral glucose lowering medication class which are mainly used for the treatment of T2D. These medications inhibit renal glucose reabsorption by inhibiting SGLT-2 expressed in the renal tubules, resulting in

significant glycosuria (Brown et al., 2021). This results in a reduction in the fat mass which leads to weight loss (Pereira & Eriksson, 2019). Recent clinical trials have shown SGLT-2 inhibitors to cause significant body weight loss, in comparison to placebo, in obese patients without T2D. Furthermore, there are also a number of comparative studies that explore the clinical superiority of the inhibitors.

## 1.1 Aims and Objectives

This study aims to evaluate the effect of SGLT-2 inhibitors in terms of weight loss in obese patients who do not have T2D, as well as compare their safety and efficacy. The objectives of the study are as follows:

- Correlate the efficacy of SGLT-2 inhibitors in weight reduction
- Explore the safety of SGLT-2 inhibitors on obese population without diabetes

The study further compares the efficacy as well as safety of Canagliflozin and Licogliflozin monotherapy in addition to co-administration of Canagliflozin and Phentermine

# Chapter 2

# Methodology

A structured literature search was carried out on PubMed and Google Scholar using various keywords such as diabetes, SGLT-2 inhibitors, overweight and without diabetes. The search yielded 8434 records. After deduplication and initial screening, the number reduced to 4758. Articles which included clinical trials investigating the safety and efficacy of SGLT-2 inhibitors on weight loss in obese patients who do not have diabetes were used. It was also ensured that the clinical trials included used the same dose as the dose for diabetes as approved by the FDA. Mendeley was used as the reference manager of choice.

The entire process, as well as the inclusion and exclusion criteria, are shown in Figure 1.

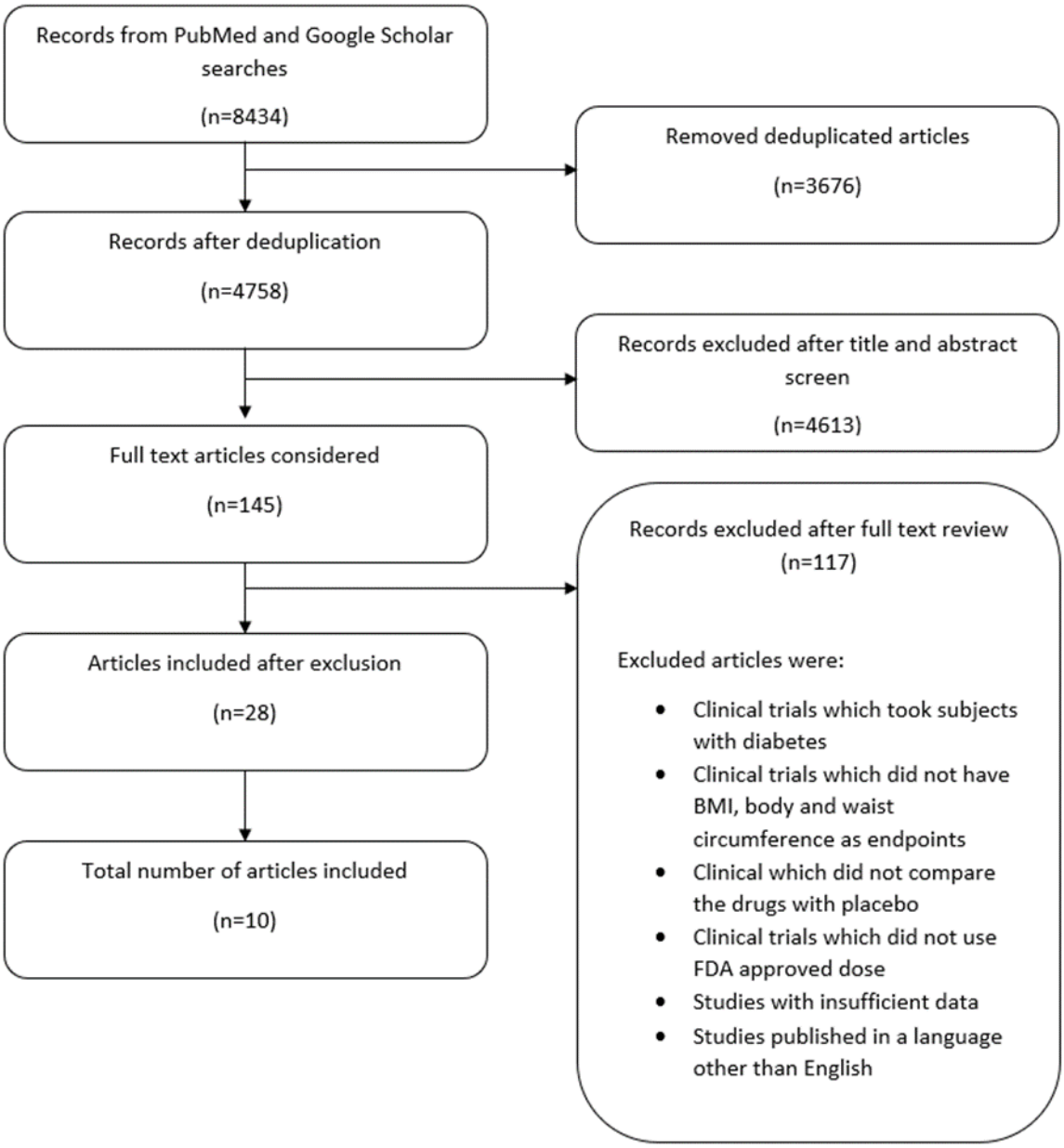


*Figure 1: Research Methodology and Workflow*

# Chapter 3

# Pharmacokinetics of SGLT-2 inhibitors

Pharmacokinetic is a crucial parameter in understanding how a drug is taken up by the body, how the drug is absorbed, how the drug and its metabolites are distributed in the body, as well as its metabolism and excretion. Table 1 below lists the pharmacokinetic properties of the SGLT-2 inhibitors.

*Table 1: Pharmacokinetic Parameters*

| Pharmacokinetic Parameters | | Canagliflozin | Licogliflozin |
|---|---|---|---|
| **Absorption** | Bioavailability | 65% | 77% |
| | $C_{max}$ | - | 1480 ng/mL (for 100 mg dose) |
| | $T_{max}$ | - | <1 |
| | AUC | - | 6050 |
| | Effect of food on bioavailability | Not affected | - |
| **Distribution** | $V_{ss}$ or $V_d$ | $V_{ss}$=83.3L | - |
| | Plasma protein binding | Yes (99%) | - |
| **Metabolism** | | Mainly metabolized in the liver by glucuronidation. | Major pathway is glucuronidation in the liver |
| **Excretion** | Clearance | 192 mL/min | - |
| | Half-life | 10.6h (for 100 mg), 13.1h (for 300 mg) | 17.2h (for 100 mg) |
| | Excretion of the drug and its metabolites | Principally in urine | 55.6% in urine, 36.9% in feces |

## 3.1. Canagliflozin

Canagliflozin 100 mg and 300 mg reached peak plasma concentrations (median $T_{max}$) in around 2 hours following a single dose (Janssen Pharmaceuticals, 1997). Dose increase is

proportional to plasma $C_{max}$ as well as AUC (Janssen Pharmaceuticals, 1997). Additionally, Canagliflozin 100 mg and 300 mg possess a terminal half-life ($t_{1/2}$) of 10.6 hours and 13.1 hours, respectively (Janssen Pharmaceuticals, 1997). After 4 to 5 days of once-daily administration, Canagliflozin achieves its steady state (Janssen Pharmaceuticals, 1997). Furthermore, Canagliflozin does not show any time-dependent pharmacokinetics; it can accumulate in the plasma following multiple doses (up to 36%) (Janssen Pharmaceuticals, 1997).

### 3.1.1 Absorption

Canagliflozin has a mean oral bio-availability of 65% (Janssen Pharmaceuticals, 1997). Studies have shown that when Canagliflozin is taken with a fatty meal, no significant effect on the pharmacokinetic properties were observed (Janssen Pharmaceuticals, 1997). Therefore, Canagliflozin can be taken with or without food (Janssen Pharmaceuticals, 1997).

### 3.1.2 Distribution

When administered intravenously Canagliflozin exhibits mean steady-state volume of distribution of 83.5 L in healthy individuals, indicating that is has extensive tissue distribution (Janssen Pharmaceuticals, 1997). Canagliflozin shows extensive protein binding in plasma, about 99% and it is mostly bounded to albumin (Janssen Pharmaceuticals, 1997). Canagliflozin concentration can affect protein binding (Janssen Pharmaceuticals, 1997). Patients with renal or hepatic impairment show no alteration in protein binding (Janssen Pharmaceuticals, 1997).

### 3.1.3 Metabolism

For Canagliflozin, *O*-glucuronidation serves as the main metabolic route. In the process, UGT1A9 and UGT2B4 are responsible for metabolizing Canagliflozin into two *O*-

glucuronide metabolites which are inactive in nature (Janssen Pharmaceuticals, 1997). CYP3A4-mediated (oxidative) metabolism plays a minor role (approximately 7%) in humans (Janssen Pharmaceuticals, 1997).

### 3.1.4 Excretion

Following a single administration of radioactive dose of Canagliflozin, it was observed that 41.5% of the dose was excreted as Canagliflozin, 3.2% as an *O*-glucuronide metabolite and 7.0% as a hydroxylated metabolite (Janssen Pharmaceuticals, 1997). A large portion of the administered radioactive drug was excreted via urine (33%), mostly as *O*-glucuronide metabolites (30.5%) (Janssen Pharmaceuticals, 1997). A very minute percentage of dose was excreted in the urine as unchanged Canagliflozin (<1%) (Janssen Pharmaceuticals, 1997). Additionally, Canagliflozin demonstrated a renal clearance of 1.30 to 1.55 mL/min for both 100 mg and 300 mg doses, respectively (Janssen Pharmaceuticals, 1997). Furthermore, the drug had a mean systemic clearance of around 192 mL/min in healthy individuals after a single administration (Janssen Pharmaceuticals, 1997).

## 3.2 Licogliflozin

In this study, only the AME of Licogliflozin is discussed. Since Licogliflozin is still under clinical trials and is yet to be approved, there is very little data available.

### 3.2.1 Absorption

In a pharmacokinetic study, 4 healthy male subjects with ages in the range of 18–45 years were given 100-mg oral dose of Licogliflozin (Wang-Lakshman et al., 2021). From the study it was observed that Licogliflozin was rapidly absorbed ($t_{max}$ < 1 h) when administered orally, and its absorption is estimated at 77% in humans and the $C_{max}$ was 1480 ng/mL following a dose of 100 mg (Wang-Lakshman et al., 2021).

### 3.2.2 Metabolism

The metabolism pathways for Licogliflozin are oxidation and glucuronidation. The major pathway observed is the direct glucuronidation, this makes up ~38% of the dose present in excreta and >29% of the dose is present in excreta (Wang-Lakshman et al., 2021).

### 3.2.3 Excretion

Licogliflozin was completely and quickly excreted, following oral administration (Wang-Lakshman et al., 2021). The amount of the radioactive drug recovered in humans was 92.5% (Wang-Lakshman et al., 2021). Licogliflozin was excreted in both urine and feces, where urinary excretion was higher (~56%) (Wang-Lakshman et al., 2021).

# Chapter 4

# Pharmacodynamics of SGLT-2 inhibitors

Pharmacodynamics is an important parameter in the identification of the target effect of a drug, as well as in the understanding its mechanism of action and the side effects.

## 4.1 Canagliflozin

Canagliflozin exhibits dose-dependent decrease in renal threshold for glucose (RTG) and increase in urinary glucose excretion for single and multiple doses (Janssen Pharmaceuticals, 1997). Canagliflozin at doses 100 mg and 300 mg q.d have a RTG suppressive effect which lasts for about 24 hour (Janssen Pharmaceuticals, 1997). The maximum suppression was observed with 300 mg, which was around 70 to 90 mg/dL (Janssen Pharmaceuticals, 1997). Patients treated with 100 mg or 300 mg of Canagliflozin demonstrated increases in the mean UGE of approximately 100g/day and this was caused by the reductions in RTG (Janssen Pharmaceuticals, 1997).

## 4.2 Licogliflozin

Licogliflozin is a dual inhibitor of both SGLT-1 and SGLT-2, thus it can follow both pathways, although it has a higher affinity for SGLT-2. Through the SGLT-1 inhibition pathway it can prevent the reuptake glucose from the renal tubules as well as prevent the uptake of sugars from the GI tract. Following the SGLT-2 pathway Licogliflozin can prevent up to 90% of glucose reabsorption.

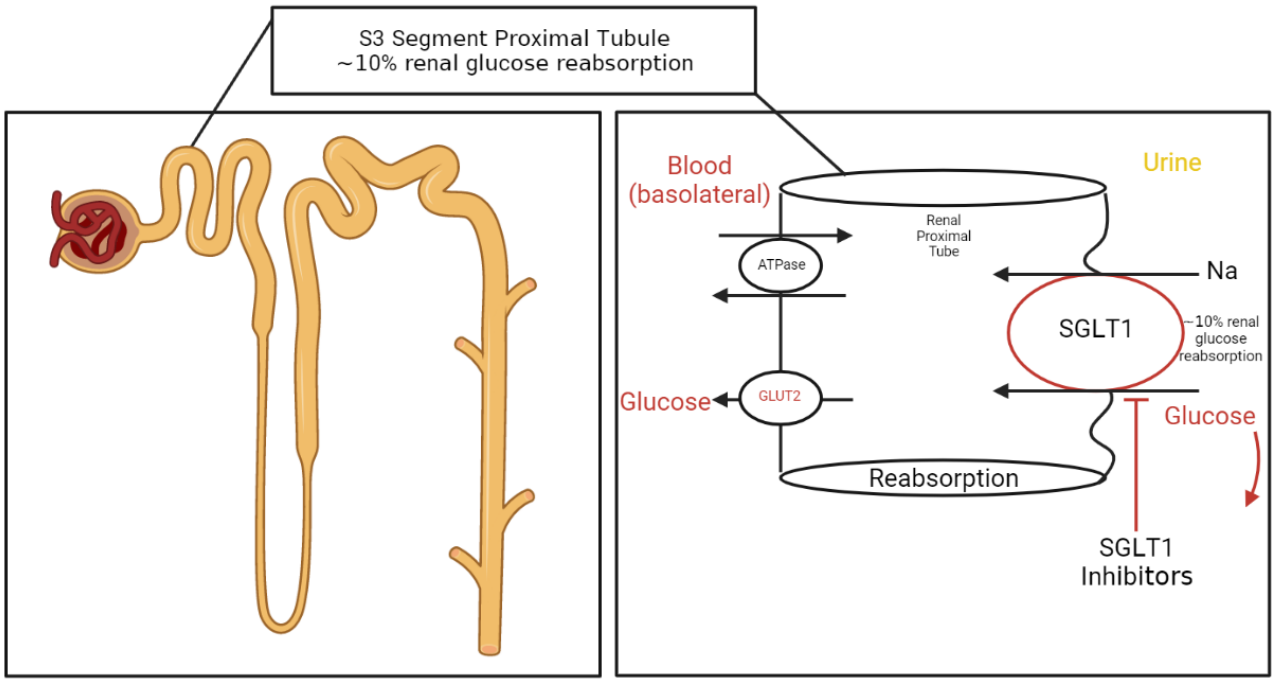


*Figure 2: Mechanism of Action of SGLT-1 inhibitor*

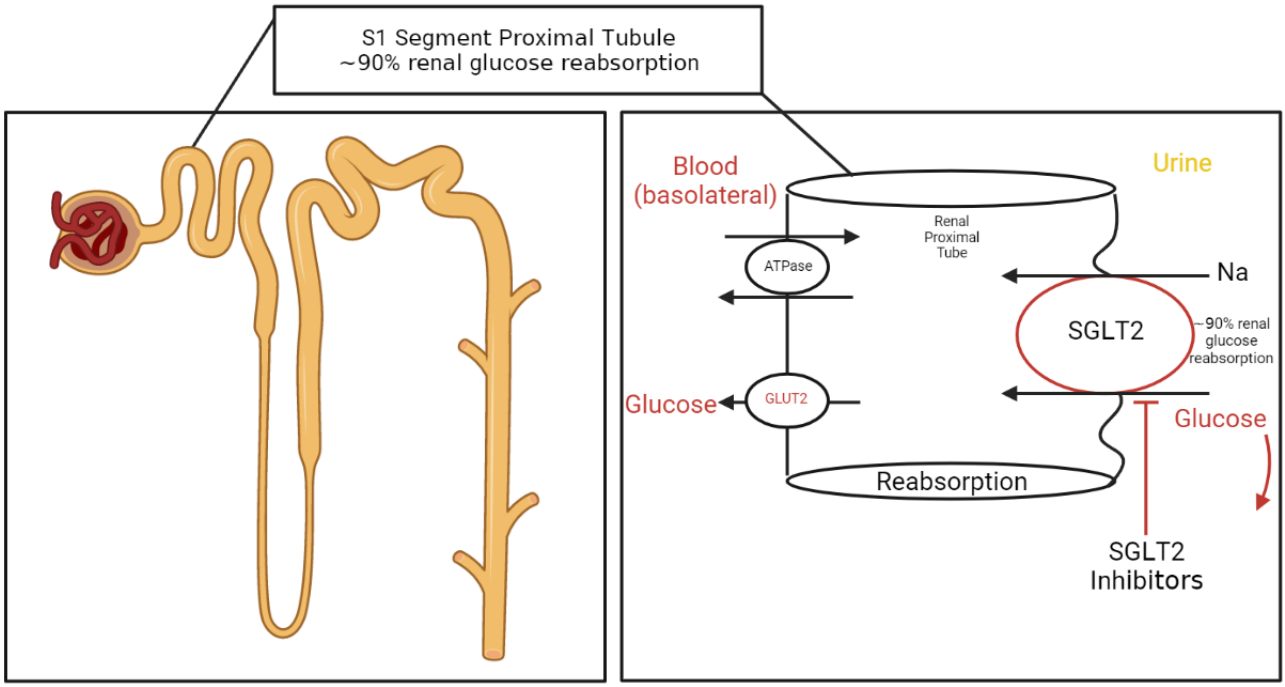


*Figure 3: Mechanism of Action of SGLT-2 inhibitor*

# Chapter 5

# Results

## 5.1 Efficacy

Efficacy is an important aspect of any medication. It gives a clear idea how the medication is working as a therapeutic agent, as well as aids in comparing effectiveness drugs of the same class. Table 2 summarizes the efficacy data obtained from the clinical trials for SGLT-2 inhibitors.

### 5.1.2 Canagliflozin

The clinical studies utilized various doses of Canagliflozin, ranging from 50 mg to 300 mg q.d. Clinical trials data shows that Canagliflozin 100 mg q.d. is more efficacious than Canagliflozin 50 mg q.d., although increasing the dose to 300 mg q.d. has diminishing effects (Bays et al., 2014).

### 5.1.3 Licogliflozin

The clinical trial used various dosage of Licogliflozin, ranging from 2.5 mg q.d to 50 mg b.i.d. Among them, the two most efficacious doses appear to be 150 mg q.d and 25mg b.i.d. The 48 week Licogliflozin versus placebo trial, demonstrated highest weight loss (5.4%) in the Licogliflozin 50 mg q.d/25 mg group (Bays et al., 2020). Licogliflozin had higher efficacy than other approved SGLT-2 inhibitors that generally lead to ~ 2% to 3.0% weight loss (Bays et al., 2020). Furthermore, the additional weight loss caused by Licogliflozin might be due its SGLT-1 inhibitory effect (Bays et al., 2020).

In the 12-week study, Licogliflozin managed to reduce waist circumference by 3.74 cm (Bays et al., 2020). Additionally, a similar reduction in waist circumference of 4.3 cm was observed with the same dose of Licogliflozin (150 mg q.d) over 24 weeks (Bays et al., 2020).

### 5.1.4 Canagliflozin/Phentermine

Results from the clinical trials indicated that co-administration of Canagliflozin/Phentermine was more efficacious than compared to monotherapy of Canagliflozin and Phentermine (Hollander et al., 2017). From the data obtained from the clinical trial, Canagliflozin (CANA), Phentermine (PHEN), co-administration of Canagliflozin and Phentermine (CANA/PHEN) and Placebo (PBO) demonstrated a LS mean percentage change of -1.9%, -4.1%, -7.5% and 0.6% in terms of body weight, respectively (Hollander et al., 2017).

Regarding decrease in body mass index (BMI), co-administration of Canagliflozin and Phentermine was the most effective. Reductions in BMI are as follows, CANA had a reduction of 0.5 $kg/m^2$, PHEN had a reduction of 1.3 $kg/m^2$, and CANA/PHEN had a reduction of 2.4 $kg/m^2$ (Hollander et al., 2017).

*Table 2: Efficacy Data from Clinical Trials*

| Article | Phase | Primary Endpoints | Secondary Endpoints | Arms/Medication | Body Weight | | BMI | | Waist circumference | |
|---|---|---|---|---|---|---|---|---|---|---|
| Bays-2014 | Phase 2b | Percentage change in body weight compared to placebo | Percentage change in BMI from base line and change in waist circumference compared to placebo. | | Mean (SD) change, (kg) | LS mean difference vs PBO (95% CI) | Mean (SD) change, kg/m2 | LS mean difference vs Placebo (95% CI), kg/m2 | Mean (SD) change, cm | LS mean difference vs PBO (95% CI) |
| | | | | Placebo | -1.1 (2.5) | | -0.4 (0.9) | | -1.2 (10.1) | |
| | | | | Canagliflozin 50 mg QD | -1.9(2.9) | -0.8 (-1.6, -0.02), P= 0.031 vs Placebo | -0.7 (1.1) | -0.3 (-0.6, -0.03), P= 0.031 vs Placebo | -1.4 (5.0) | -0.3 (-2.7, 2.2) |
| | | | | Canagliflozin 100 mg QD | -2.8 (2.9) | -1.6 (-2.4, -0.8), P≤0.001 vs Placebo | -1.0 (1.0) | -0.6 (-0.9, -0.3), P ≤ 0.001 vs Placebo | -2.9 (10.3) | -0.9 (-3.5, 1.6) |
| | | | | Canagliflozin 300 mg QD | -2.4 (2.9) | -1.3 (-2.1, -0.5), P≤0.001 vs Placebo | -0.9 (1.1) | -0.5 (-0.8, -0.2), P ≤ 0.001 vs Placebo | -2.6 (7.2) | -1.4 (-3.8, 1.1) |

| Article | Phase | Primary Endpoints | Secondary Endpoints | Arms/Medication | Body Weight | | | | Waist circumference | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Placebo-subtracted change from baseline (kg) | | Dose response | | Adjusted mean change (95% CI) | | Comparison of adjusted mean changes: Licogliflozin vs. placebo | | |
| | | | | | Model-based | 95% CI | Model-based | 95% CI | Licogliflozin | Placebo | Difference (Licogliflozin-placebo) | 95% CI | Two-sided P |
| Bays-2020 | | Percent change from baseline in body weight following treatment with four once-daily doses of Licogliflozin or four twice-daily doses of Licogliflozin (versus placebo). | Response rates according to percent decrease in body weight; and effect of Licogliflozin versus placebo on waist circumference. | Placebo | | | −0.63 | −1.56 to 0.37 | | −1.3 (−2.54 to −0.05) | | | |
| | | | | Licogliflozin 2.5 mg qd | −0.45 | −2.26 to 0.00 | −1.24 | −2.50 to −0.45 | −2.1 (−3.87 to −0.31) | −1.3 (−2.54 to −0.05) | −0.8 | −2.96 to 1.37 | 0.47 |
| | | | | Licogliflozin 10 mg qd | −1.38 | −3.21 to −0.06 | −2.04 | −3.36 to −0.88 | −2.7 (−4.55 to −0.92) | −1.3 (−2.54 to −0.05) | −1.4 | −3.64 to 0.76 | 0.199 |
| | | | | Licogliflozin 50 mg qd | −2.93 | −4.39 to −0.78 | −3.52 | −4.62 to −1.87 | −3.7 (−5.55 to −1.82) | −1.3 (−2.54 to −0.05) | −2.4 | −4.63 to −0.15 | 0.037 |
| | | | | Licogliflozin 150 mg qd | −3.73 | −5.04 to −2.49 | −4.37 | −5.36 to −3.37 | −5.6 (−6.84 to −4.35) | −1.3 (−2.54 to −0.05) | −4.3 | −6.06 to −2.54 | <0.001 |
| | | | | Licogliflozin 2.5 mg bid | −0.87 | −2.16 to 0.00 | −1.67 | −2.61 to −0.27 | −2.7 (−4.47 to −0.91) | −1.3 (−2.54 to −0.05) | −1.4 | −3.56 to 0.77 | 0.206 |
| | | | | Licogliflozin 5 mg bid | −1.96 | −3.54 to −0.33 | −2.51 | −3.94 to −1.32 | −4.3 (−6.07 to −2.57) | −1.3 (−2.54 to −0.05) | −3.0 | −5.18 to −0.88 | 0.006 |
| | | | | Licogliflozin 25 mg bid | −3.52 | −5.06 to −1.63 | −4.06 | −5.52 to −2.87 | −4.8 (−6.61 to −2.98) | −1.3 (−2.54 to −0.05) | −3.5 | −5.70 to −1.30 | 0.002 |
| | | | | Licogliflozin 50 mg bid | −3.83 | −5.26 to −2.48 | −4.47 | −5.49 to −3.48 | −4.6 (−5.89 to −3.31) | −1.3 (−2.54 to −0.05) | −3.3 | −5.10 to −1.51 | <0.001 |

| Article | Phase | Primary Endpoints | Secondary Endpoints | Arms/ Medications | Body weight | | | | | | | | | | BMI | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | mITT analysis set | | | | | per-protocol analysis set | | | | | | | |
| | | | | | Mean ± SD baseline, kg | LS mean ± SE percent change | Difference (95% CI) vs PBO | LS mean ± SE change, kg | Difference (95% CI) vs PBO | Mean ± SD baseline, kg | LS mean ± SE percent change | Difference (95% CI) vs PBO | LS mean ± SE change, kg | Difference (95% CI) vs PBO | Mean ± SD baseline, kg/m2 | LS mean ± SE change | Difference (95% CI) vs PBO |
| Hollander-2017 | | Percent change from baseline in body weight with CANA/PHEN versus PBO at week 26. | Key secondary end points were the change of BMI from baseline compared to placebo. | Placebo | 104.0 ± 18.3 | –0.6 ± 0.6 | | –0.6 ± 0.6 | | 104.2 ± 17.9 | –1.1 ± 0.7 | | –1.0 ± 0.8 | | 37.8 ± 5.1 | –0.2 ± 0.2 | |
| | | | | Canagliflozin | 103.3 ± 19.6 | –1.9 ± 0.6 | –1.3 (–3.1, 0.4) | –1.9 ± 0.7 | –1.3 (–3.1, 0.5) | 105.1 ± 20.0 | –2.6 ± 0.7 | –1.5 (–3.4, 0.4) | –2.6 ± 0.7 | –1.6 (–3.6, 0.4) | 37.2 ± 4.8 | –0.7 ± 0.2 | –0.5 (–1.1, 0.2) |
| | | | | Phentermine | 102.4 ± 18.6 | –4.1 ± 0.6 | –3.5 (–5.3, –1.8) | –4.1 ± 0.6 | –3.5 (–5.3, –1.7) | 102.5 ± 19.0 | –4.6 ± 0.7 | –3.4 (–5.3, –1.5) | –4.5 ± 0.7 | –3.5 (–5.5, –1.6) | 37.0 ± 5.6 | –1.5 ± 0.2 | –1.3 (–1.9, –0.7) |
| | | | | Canagliflozin plus Phentermine | 100.1 ± 18.1 | –7.5 ± 0.6 | –6.9 (–8.6, –5.2) | –7.3 ± 0.6 | –6.7 (–8.5, –4.9) | 98.1 ± 15.3 | –8.1 ± 0.7 | –7.0 (–8.9, –5.1) | –8.0 ± 0.7 | –7.0 (–8.9, –5.1) | 36.6 ± 5.4 | –2.6 ± 0.2 | –2.4 (–3.1, –1.8) |

## 5.2 Safety

### 5.2.1 Safety Data from Clinical Trials

Safety data from clinical trials are important as it helps us to observe which adverse effects are more prevalent and occur more frequently and determine whether or not the drug is suitable for use. Table 3 summarizes the safety data obtained from the clinical trials.

#### 5.2.1.1 Canagliflozin

In the clinical trial, the overall side effects were similar for each group. No major and serious side effects were observed. Canagliflozin had higher incidences of nausea, sinusitis and vulvovaginal mycotic infection among the other common side effects, although their intensity was mild or moderate. Females experienced higher incidence of genital mycotic infection than men who had received the same dose of Canagliflozin (14% for CANA 50mg, 13% for CANA 100mg and 19% for CANA 300mg) (Bays et al., 2014). There was only a single case of male genital mycotic infection with 300 mg Canagliflozin (Bays et al., 2014). The cases of UTIs were similar across all the groups (10% for CANA 50mg, 8% for CANA 100mg and 8% for CANA 500mg) (Bays et al., 2014). Incidences of osmotic diuresis related adverse effects (4% for CANA 50mg, 2% CANA 100mg and 4% CANA 300mg) and symptomatic hypoglycemia were low across all groups (Bays et al., 2014).

#### 5.2.1.2 Licogliflozin

In the clinical study it was observed that Licogliflozin has good tolerability, although a small proportion of subjects stopped during the initial 24 weeks due to the occurrence of adverse effects (Bays et al., 2020). Among the adverse effects, musculoskeletal and connective tissue disorders (8%-24%), gastrointestinal disorders (33%-68) and different types of infections and infestations (21%-45%) had the highest incidence rate (Bays et al., 2020). GI related adverse

effects like diarrhea (16%-69%) and flatulence (13%-37%) occurred across all the doses and appeared to be dose related (Bays et al., 2020). Adverse effects of special interest had an overall low frequency across all treatment groups (Bays et al., 2020). There were zero cases hypoglycemia as well ketoacidosis (Bays et al., 2020). Additionally, there was low incidence of urinary tract infections (1.3%-10.3%) and impaired renal function (0%-7.9%) (Bays et al., 2020).

#### 5.2.1.3 Canagliflozin/Phentermine

Placebo (PBO), Canagliflozin (CANA), Phentermine (PHEN) and co-administration of Canagliflozin/Phentermine (CANA/PHEN) had 57.3%, 59.5%, 54.1% and 66.3% of incidence rate, respectively (Hollander et al., 2017). There were no cases male genital mycotic infections, treatment-emergent fractures, renal- or photosensitivity-related adverse effects, or adverse effects of diabetic ketoacidosis or related events (Hollander et al., 2017). Female genital mycotic infections had 10.3% incidence rate with CANA and 7.2% incidence rate with CANA/PHEN (Hollander et al., 2017). There were no incidences of female genetic mycotic infections with PBO and PHEN (Hollander et al., 2017). Apart from one severe event with CANA, majority of these events moderate in intensity (Hollander et al., 2017). In the case of UTIs, there was an overall low incidence, but CANA and CANA/PHEN had higher incidence when compared to PBO and PHEN (4.8%, 2.4%, 0% and 1.2%), respectively (Hollander et al., 2017). All reported UTIs were moderate in nature and there were no cases of upper UTIs in any group (Hollander et al., 2017).

*Table 3: Safety Data from Clinical Trials*

| Adverse Effects | Licogliflozin | | | | | | | | Canagliflozin | | | Canagliflozin/Phentermine |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2.5 mg qd | 10 mg qd | 50 mg qd | 150 mg qd | 2.5 mg bid | 5mg bid | 25 mg bid | 50 mg bid | 50 mg qd | 100 mg qd | 300 mg qd | 300 mg/15 mg qd |
| Diarrhea | 7/38 (18.4) | 6/38 (15.8) | 21/38 (55.3) | 53/77 (68.8) | 10/38 (26.3) | 8/39 (20.5) | 15/38 (39.5) | 43/76 (56.6) | 5/98 (5) | 3/93 (3) | 2/96 (2) | - |
| Constipation | 3/38 (15.8) | 4/38 (10.5) | 7/38 (18.4) | 10/77 (13.0) | 12/38 (31.6) | 5/39 (12.8) | 6/38 (15.8) | 9/76 (11.8) | 5/98 (5) | 3/93 (3) | 2/96 (2) | - |
| Nausea | 1/38 (2.6) | 3/38 (7.9) | 4/38 (10.5) | 4/77 (5.2) | 6/38 (15.8) | 2/39 (5.1) | 2/38 (5.3) | 6/76 (7.9) | 7/98 (7) | 6/93 (6) | 3/96 (3) | - |
| Abdominal pain | 2/38 (5.3) | 2/38 (5.3) | 3/38 (7.9) | 7/77 (9.1) | 3/38 (7.9) | 3/39 (7.7) | 4/38 (10.5) | 9/76 (11.8) | - | - | - | - |
| Genital mycotic infection | | | | | | | | | | | | |
| Men | - | - | - | - | - | - | - | - | 0 | 0 | 0 | 0 |
| Women | - | - | - | - | - | - | - | - | 12/86 (14) | 10/76 (13) | 19/86 (22) | 5/69 (7.2) |
| Urinary tract infection | - | - | - | - | - | - | - | - | 10/98 (10) | 7/93 (8) | 8/96 (8) | 2/83 (2.4) |
| Osmotic diuresis–related AEs | - | - | - | - | - | - | - | - | 3/98 (3) | 3/93 (3) | 4/96 (4) | 8/83 (9.6) |
| Dizziness | - | - | - | - | - | - | - | - | 4/98 (4) | 2/93 (2) | 4/96 (4) | 0 |
| Hypoglycemia | - | - | - | - | - | - | - | - | 1/98 (1) | 0 | 2/96 (2) | - |
| Nasopharyngitis | 2/38 (5.3) | 3/38 (7.9) | 2/38 (5.3) | 5/77 (6.5) | 3/38 (7.9) | 3/39 (7.7) | 4/38 (10.5) | 4/76 (5.3) | 6/98 (6) | 1/93 (1) | 1/96 (1) | - |
| Gastrointestinal motility disorder | 2/38 (5.3) | 1/38 (2.6) | 2/38 (5.3) | 4/77 (5.2) | 6/38 (15.8) | 0 | 2/38 (5.3) | 3/76 (3.9) | - | - | - | - |

### 5.2.2 Safety data from FAERS Database

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products.

Safety data obtained from FAERS database can be used to correlate safety data from clinical trials and the different adverse effects reported after a drug is launched into the market. The clinical trials selected in the current study were taken using the same dose approved by FDA for the treatment of T2D. Table 4 contains the safety data obtained from the FAERS database (2022-2012) for SGLT-2 inhibitors.

*Table 4: Safety Data form FAERS Database*

| Adverse Effects | Canagliflozin | Licogliflozin | Canagliflozin/Phentermine |
|---|---|---|---|
| Osmotic Diuresis related AEs | 294/6855 (4.29%) | - | - |
| Volume Depletion Related AEs | 177/6855 (2.58%) | - | - |
| Genital Mycotic Infection | 89/6855 (1.30%) | - | - |
| Hypoglycemia | 40/6855 (0.58%) | - | - |
| Urinary Tract Infection | 280/6855 (4.08%) | - | - |
| GI Related Problems | 141/6855 (2.06%) | - | - |
| Other AEs: | | | |
| Necrosis | 132/6855 (2%) | - | - |
| Insomnia | 20/6855 (0.3%) | - | - |
| Depression | 17/6855 (0.25%) | - | - |
| Cardiac Failure | 35/6855 (0.51%) | - | - |

*Table 5: Safety Data from Package Insert*

| Adverse Effects | Licogliflozin | Canagliflozin | | Canagliflozin/Phentermine |
|---|---|---|---|---|
| | | 100mg | 300mg | |
| Nausea | - | 2.20% | 2.30% | - |
| Diarrhea | - | - | - | - |
| Decreased Appetite | - | - | - | - |
| Vomiting | - | - | - | - |
| Constipation | - | 1.80% | 2.30% | - |

| | | | | |
|---|---|---|---|---|
| Dyspepsia | - | - | - | - |
| Abdominal Pain | - | - | - | - |
| Female genital mycotic infections | - | 10.40% | 11.40% | - |
| Urinary tract infections | - | 5.90% | 4.30% | - |
| Increased urination | - | 5.30% | 4.60% | - |
| Male genital mycotic infections | - | 4.20% | 3.70% | - |
| Vulvovaginal pruritus | - | 1.60% | 3.00% | - |
| Thirst | - | 2.80% | 2.30% | - |

#### 5.2.2.1 Canagliflozin

By its very nature, the mechanism of action of SGLT-2 inhibitors cause a rise in UGE which is its major safety concern (Halimi & Vergès, 2014). This can lead to adverse effects such as increased urinary frequency, urinary tract infection, electrolyte imbalances and genital infections (Halimi & Vergès, 2014). Since SGLT-2 inhibitors increase the glucose excretion rate, there is a potential to promote fungal growth in the genitourinary tract (Halimi & Vergès, 2014). Women are more prone to genital mycotic infection than compared to men (by four to five times) this is due to women having shorter urethras when compared to men (Halimi & Vergès, 2014).

Safety data obtained from FAERS database (2022-2012) for Canagliflozin shows that 1.30% of cases of adverse effects are due genital mycotic infections and all of these patients are females. This also coincides with the safety data from the package insert for Canagliflozin, where women have a higher percentage of experiencing genital mycotic infection than men.

UTIs in general are another common side effect of SGLT-2 inhibitors. This is again due the mechanism of action of the drugs. Due to the increase in glucose excretion via the urine, small amounts of glucose remain inside the urethra, this establishes an environment which

promotes microbial growth (Halimi & Vergès, 2014). The clinical trials which have been looked at in this study, UTIs have shown up as a frequently common adverse effect.

The safety data obtained from FAERS database, Canagliflozin has a 4.08% incidence rate for UTIs. This also coincides with the safety data obtained from the package insert

From the FAERS safety data it can be observed that Canagliflozin has a 2.06% incidence rate for GI related problems. This coincides with the safety data obtained from the package inserts

Since SGLT-2 inhibitors increase the overall rate of excretion glucose via frequent urinations. This lowers the water content in the body, resulting in side effects like thirst, dry mouth etc. From the safety data obtained from FAERS database, it can be seen that Canagliflozin has a 4.29% incidence rate for osmotic diuresis related adverse effects, the same trend can be observed when looking at the safety data obtained from the package insert.

The most common volume depletion related adverse effect is dizziness. Volume depletion is related to osmotic level of the body. From the data obtained from FAERS database it can be seen that Canagliflozin has a 2.58% incidence rate for volume depletion related adverse effects.

Hypoglycemia has an overall low incidence. From the safety data obtained from FAERS, Canagliflozin has a 0.58% incidence rate.

Searching the FAERS database a few adverse effects were identified for Canagliflozin which were not included in the clinical trials. These include necrosis which had a 2% incidence rate, insomnia 0.3% incidence rate and cardiac events 0.5%. Further clinical trials and post marketing data are required to determine the significance of these adverse effects.

#### 5.2.2.2 Licogliflozin

Since the drug has not yet been approved by the FDA, there was no safety data available in the FAERS database.

#### 5.2.2.3 Canagliflozin/Phentermine

There was no safety data available on the FAERS database as FDA has not yet approved the co-administration of Canagliflozin and Phentermine.

# Chapter 6

# Conclusion

The clinical trial data of the sodium glucose cotransporter 2 (SGLT-2) inhibitors (Canagliflozin, Licogliflozin, and co-administration of Canagliflozin and Phentermine) suggest that they could be used to treat obesity, in addition to their approved use for Type 2 Diabetes (T2D). The study found the co-administration of Canagliflozin and Phentermine to be most efficacious among the three SGLT-2 inhibitors. This is based on the efficacy data obtained from the clinical trials that include percentage of reduction in body weight, percentage reduction in BMI and reduction in waist circumference. Canagliflozin can be suggested to be the safest drug, based on the study of the safety data obtained from the clinical trials and safety data obtained from FAERS database, urinary tract infection and genital mycotic infection were the parameters.

Based on the literature search and current study of sodium glucose cotransporter 2 (SGLT-2) inhibitors, it is evident that urinary tract infection and genital mycotic infections are some of the most common and major adverse effects. Clinicians need to be aware of these adverse effects when prescribing the SGLT-2 inhibitors. If any patient experiences any of these adverse effects, they need to report it immediately to their clinician. Exploring different combination therapy with SGLT-2 inhibitors and well-established weight reduction regime/medications and comparing their safety and efficacy with SGLT-2 monotherapy is another potential area. Further clinical trials can investigate the effectiveness and safety of dual SGLT-1/2 inhibitors and SGLT-2 inhibitors.

Overall, SGLT-2 inhibitors (Canagliflozin, Licogliflozin) may be us to obesity. However more clinical trials and post marketing data are required to determine the safety and efficacy of these emerging class of drugs.

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