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A Comparison of the Safety and Efficacy of Sotagliflozin and Baxaglifloxin in the Treatment of Type II Diabetes Mellites. A systemic review and Meta-analysis.

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Abstract**—** *The effectiveness of Sotagliflozin (200 mg) and Bexagliflozin (20 mg) was evaluated based on HbA1c levels and fasting plasma glucose levels of the participants. Changes in blood pressure and body weight were assessed as secondary outcomes. Regarding safety, adverse events such as genital mycotic infections, urinary tract infections (UTIs), and hypoglycemia were assessed. This meta-analysis showed that Bexagliflozin (20 mg) is more efficient in managing Type 2 Diabetes mellitus than Sotagliflozin (200 mg), in terms of reductions in HbA1c levels, FPG and SBP. This study also showed that the incidence of adverse events was lower with Bexagliflozin. Bexagliflozin showed a greater reduction of HbA1C levels with a mean reduction of -0.63 (-0.65, -0.62); P <0.00001 and Sotagliflozin showed a mean reduction of -0.03 (-0.04, -0.02); P <0.00001. Bexagliflozin showed a mean reduction in FPG of -1.07 (-1.13, -1.02); P <0.00001 while, Sotagliflozin showed a mean reduction of -0.75 (-0.78, -0.72); P <0.00001. Bexagliflozin had a greater mean reduction in the Systolic BP of -2.86 (-3.18, -2.55); P <0.00001, while Sotagliflozin showed a mean reduction of -2.40 (-2.54, -2.27); P <0.00001. Sotagliflozin showed a greater mean reduction in the body weights of -1.67 (-1.73, -1.62); P <0.00001, and Bexagliflozin had a mean reduction of -1.50 (-1.57, -1.43); P <0.00001. Both drugs were seen to be safe when taken orally. Most commonly seen adverse effects in both groups were Hypoglycemia, Genital Mycotic infections and, Urinary Tract Infections. Hypoglycemia was seen almost equally in both Sotagliflozin patients (RR: 1.05 (0.88, 1.26)) and Bexagliflozin (RR: 0.98 (0.73, 1.33)). Sotagliflozin increased the risk of genital mycotic infection – (RR: 2.14 (0.48, 9.50)) in contrast to Bexagliflozin - RR: 0.46 (0.09, 2.32). Bexagliflozin was found to predispose the patients to UTIs (RR: 2.88 (1.41, 5.86)) in contrast to Sotagliflozin with RR: 0.97 (0.70, 1.34).*

Keywords**—** *Sotagliflozin; Bexagliflozin; Sodium-glucose co-transporter (SGLT); Efficacy; Safety; Type 2 diabetes mellitus; meta-analysi.*

I. INTRODUCTION

Tignificant portions of the global population is facing a serious threat from diabetes. Simply put, Diabetes Mellitus (DM) is a condition characterized by poor regulation of blood glucose levels. From a scientific perspective, DM is a metabolic disorder that leads to a chronic state of high blood sugar and is caused by abnormalities in the production or action of insulin. Type 2 DM is characterized by abnormalities in the action of insulin leading to elevated blood sugar levels. The incidence of type 2 diabetes mellitus has shown a steep upward trend in recent times and has now reached alarmingly high levels. According to the International Diabetes Foundation, there are currently 366 million people with diabetes worldwide, and this number is projected to rise to 552 million by 2030 [(1)]. Current Type 2 DM medications primarily focus on managing blood sugar levels by altering glucose and glycogen metabolism. These Medications are associated with well-known undesirable side effects, such as weight gain and severe hypoglycemia, which in turn leads to an increase in the risk of cardiovascular events. These statistics highlight the urgent need for a diabetes management strategy to address existing gaps in DM management.

Recent trends focus on the family of drug targets known as sodium-dependent glucose co-transporters (SGLTs) Inhibitors [(7)]. SGLTs are predominantly found in the proximal tubules of the kidneys and play a crucial role in reabsorbing glucose from the filtered blood. SGLT1 is responsible for absorbing glucose and galactose in the digestive system, while SGLT2, found in the kidneys, reabsorbs approximately 90% of the filtered glucose [(2)]. In the case of individuals with type 2 diabetes mellitus (T2DM), inhibiting the SGLT2-mediated reabsorption of glucose and inhibition of SGLT1-mediated glucose absorption have emerged as a unique and highly effective treatment option for controlling high blood sugar levels.

Sotagliflozin, the first of its kind, is a dual inhibitor of SGLT1 and SGLT2. Studies have shown that Sotagliflozin exerts its effects by inhibiting intestinal SGLT1, slowing down glucose absorption, and consequently lowering postprandial glucose levels, as well as inhibiting renal SGLT2 and increasing the excretion of glucose through urine [(4)]. On April 26, 2019, the European Medicines Agency (EMA) approved Sotagliflozin, marketed as "ZYNQUISTA," for the treatment of type 1 diabetes and type 2 diabetes mellitus [(26)].

Bexagliflozin is a selective and potent inhibitor of SGLT2 [(5)]. It inhibits the reabsorption of glucose in the kidneys by targeting SGLT2, leading to increased excretion of glucose in the urine and lower blood glucose levels, irrespective of insulin sensitivity [(6)]. The U.S. Food and Drug Administration (FDA) granted authorization for Bexagliflozin in January 2023 for the management of type 2 diabetes in adults. It is marketed under

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the name of "BRENZAVVY" for the treatment of type 2 diabetes. [25]

This study aims to compare the safety and effectiveness of Sotagliflozin and Bexagliflozin in the management of diabetes mellitus.

II. METHODOLOGY

- *Search Strategy:*

For this meta-analysis, multiple databases were utilized, including PubMed, Embase, MEDLINE, Google Scholar, and ClinicalTrials.gov. A combination of free-text terms and medical subject headings (MeSH) were used to conduct the search. The main keywords employed in the search included "Sotagliflozin," "LX4211," "Baxaglifloxin," "diabetes mellitus," "hypoglycemia," "body weight," "Blood pressure," and "safety." Further, a manual review of the references cited in the relevant literature was also conducted.

- *Inclusion and Exclusion Criteria:*

The inclusion criteria for this study involved selecting English reports of completed clinical randomized controlled trials (RCTs) that specifically examined the efficacy and safety of Sotagliflozin (200 mg) and Bexagliflozin (20 mg) in the treatment of diabetes mellitus (DM). The included articles were required to be placebo-controlled RCTs, and Sotagliflozin and Bexagliflozin had to be involved in either phase II or phase III of the trials. Additionally, the articles needed to explicitly mention adverse events related to the use of these medications.

The exclusion criteria for this study involved excluding studies that included inappropriate subgroup analysis or single-arm treatment. Research that was not placebo-controlled was also excluded. Articles that did not report adverse events were not considered. Additionally, research data that could not be extracted was excluded from the analysis. In the case of duplicate articles, the latest article would be selected and reviewed.

- *Outcome Measures:*

The outcome measures of the study focused on several factors related to the management of diabetes. These included the effectiveness of Sotagliflozin and Bexagliflozin in controlling blood sugar levels, as well as monitoring the occurrence of associated negative events such as instances of volume depletion. Additionally, the study also assessed factors such as reduction in body weight and similar outcomes for both Sotagliflozin and Bexagliflozin

- *Data Extraction:*

The review process involved one investigator, namely Rajanigandha Dutt, who independently conducted the review. The study's baseline information comprises key details, including the author(s)' name, publication year, the country of study conduct, medication regimens administered to the experimental and control groups, the total number of participants in the study, and the adverse events observed and reported throughout the research. The baseline data encompasses information on the author, publication year, country, drug regimens for both experimental and control groups, participant count, and any adverse events noted during the trial.

- *Risk of Bias Assessment:*

In this study, the potential risks of bias in the trials were assessed using the Cochrane Collaboration Risk of Bias Assessment tool [27]. This tool looks at several factors, such as sequence generation, allocation concealment, blinding, inadequate outcome data, selective result reporting, and the presence of any additional potential biases. This tool was employed to evaluate the methodological quality and potential sources of bias in the included trials.

- *Statistical Assessments:*

In this study, The Reviewer Manager 5.4 Software was used to perform the analyses. All the performed analyses used a fixed effects model. A 95% Confidence Interval was also set for the analysis. The continuous variables were assessed as mean differences with a fixed effects model and the inverse variance method was used. The report was then provided in terms of mean reduction. The results reported in dichotomous outcomes were analyzed to provide the risk ratio, and the same was reported.

III. RESULTS

A primary search using the previously specified search method yielded a total of 146 studies. (Bexagliflozin 27 and Sotagliflozin 119). 53 of the aforementioned studies were RDCPT and were evaluated for further review. The strict screening criteria excluded any papers that used unsuitable subgroup analysis or single-arm studies that were not in phase II or phase III clinical trials had unextractable data or were for secondary analysis. A total of eight studies were found to be appropriate for the current analysis. Four of the eight included studies used Sotagliflozin (200 mg) as an intervention and four used Bexagliflozin (20 mg) as an intervention. This included 2833 individuals (1738 on Sotagliflozin and 1094 on Bexagliflozin). The patients in the studies had previously been diagnosed with Type II DM. The studies were RDPCTs, with two being Phase II trials and six being Phase III trials. The experimental arm received either 200 mg of Sotagliflozin (n=4) or 20 mg of Bexagliflozin (n=4), whereas the control arm received a placebo. Studies included for Sotaglifloxin were all phase 3 trials (David et al 2022, David et al 2017, Suman Watson et al 2021 and Suman Watson et al 2017). They were all RDPCTs and assessed the patients at a minimum of 24 weeks. Studies included for Bexagliflozin were Phase 2 (Yuan-Di C. Halvorsen et al and J. Paul Lock et al_2) and Phase 3 (Andrew S. Allegretti et al and J. Paul Lock et al). They were all RDPCTs and assessed the patients at a minimum of 24 weeks

Effect Of Sotagliflozin and Bexagliflozin on HBA1C Levels:

Out of the included studies, eight provided the necessary data on HbA1c, comprising a total of 1105 patients in the active arms and a total of 1066 patients in the control arms.

Among these, four studies focused on patients receiving SGL, with a total of 589 patients in the active arm and 629 patients in the control arm. On average, participants were

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analysed at the 24-week mark. The mean reduction of these four studies was -0.03 HbA1c%; (P < 0.00001) (Fig 1). Sotagliflozin demonstrated a favourable impact on reducing HbA1c levels, although the maximum effects were observed over a longer duration, as noted in the studies by David Z. I. Cherney et al. in 2022 and 2017, where better reductions were observed over 52 weeks.

Four out of the eight studies focused on BGL, involving 516 total patients in the active arm and 437 patients in the control arm. HbA1c levels were analysed over 24 weeks. The mean reduction of these four studies was -0.63 HbA1c%; (P < 0.00001) (Fig 1). Bexagliflozin exhibited a more immediate effect on the patients' HbA1c levels, which persisted even with continued administration, as seen in the study by Yuan-Di C. Halvorsen et al. in 2019.

When comparing the two drugs, Bexagliflozin displayed a more pronounced effect on HbA1c levels compared to Sotagliflozin. Bexagliflozin also demonstrated a more immediate impact on HbA1c levels, while Sotagliflozin required longer durations of administration to show significant changes.

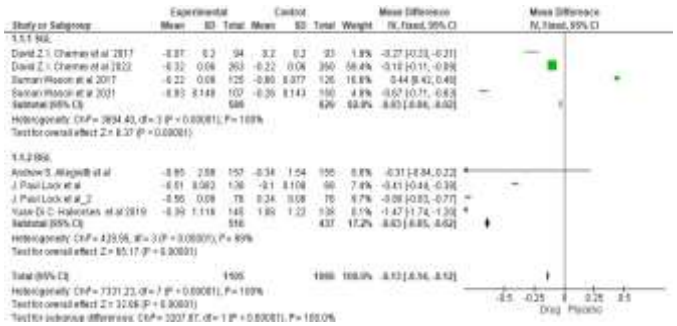

Fig. 1. Effect of SGL Vs BGL on HbA1c Levels

Effect of Sotagliflozin and Bexagliflozin on Fasting Plasma Glucose (Fpg) Levels:

A total of five studies provided data on Fasting Plasma Glucose (FPG) levels, encompassing 747 patients in the active arms and 668 patients in the control arms.

Among these studies, two focused on patients receiving SGL. These studies analysed FPG levels in a total of 388 patients in the active arm and 386 patients in the control arm over 24 weeks. The results demonstrated that Sotagliflozin rapidly reduced FPG levels, a mean reduction of -0.75 mmol/dL; (P < 0.00001) (Fig 2). Furthermore, the studies indicated that the improvements achieved at the end of 24 weeks were sustained up to week 52.

Three studies included data on FPG levels of patients on Bexagliflozin. In these studies, 359 patients in the active arm and 282 patients in the control arm were analysed. The overall effect showed a mean reduction of -1.07 mmol/dL; (P < 0.00001) (Fig 2). The results obtained at the 24-week mark were maintained for up to 96 weeks, as observed in the study by Yuan-Di C. Halvorsen et al. in 2019.

Effect of Sotagliflozin and Bexagliflozin on Body Weight:

Six studies included in the analysis investigated the impact of the two drugs on body weight reduction as an outcome with an overall total of 854 patients in the active arms and 818 patients in the control arms.

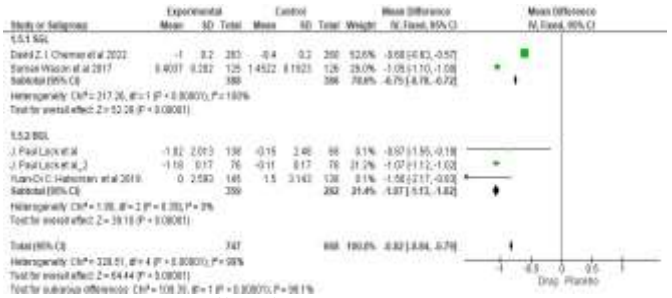

Fig. 2. Effect of SGL Vs BGL on FPG Levels

Among these studies, three focused on Sotagliflozin, involving 495 patients in the active arm and 536 patients in the control arm. Over 24 weeks, Sotagliflozin demonstrated superior efficacy in reducing body weight. However, by the 56-week mark, the reduction in body weight seemed to have stabilized, showing no significant additional changes. The mean reduction observed in these studies was -1.62 kg; (P < 0.00001) (Fig 3).

Three studies analysed the effect of Bexagliflozin on body weight, encompassing 359 patients in the active arm and 282 patients in the control arm. Unlike Sotagliflozin, Bexagliflozin consistently resulted in reductions in body weight that did not exhibit substantial changes over time. This trend was observed in the study conducted by Yuan-Di C. Halvorsen et al. in 2019. The mean reduction in body weight reduction was found to be -1.50 kg (P < 0.00001) (Fig 3).

When comparing the two drugs, Sotagliflozin demonstrated greater efficacy in reducing body weight over 24 weeks, while Bexagliflozin showed a consistent and stable effect on body weight reduction over time.

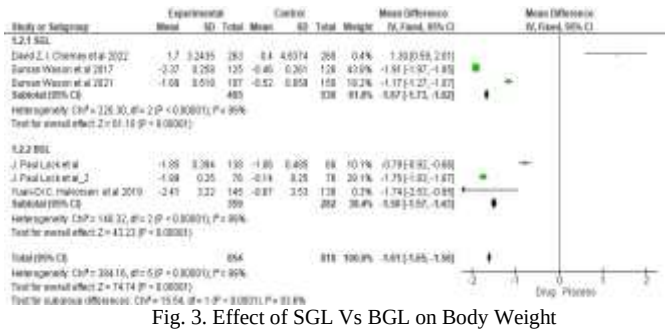

Fig. 3. Effect of SGL Vs BGL on Body Weight

Effect of Sotagliflozin and Bexagliflozin on Blood Pressure:

Six of the included studies provided data on systolic blood pressure (SBP)with a total of 854 patients in the active arms and 818 patients in the control arms.

Among these studies, 495 patients were in the Sotagliflozin active arm, while 536 patients were in the control arm. It was noted in the studies by David Z. I. Cherney et al. in 2022 and 2017 that changes in SBP were not observed in patients with a baseline SBP greater than 130 mmHg. However, reductions in SBP were observed in patients receiving Sotagliflozin, with a mean reduction of -2.40 mmHg (P < 0.00001) (Fig 4). It was noted in the studies that changes in DBP in patients receiving

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Sotagliflozin were not clinically significant.

Bexagliflozin was found to have a greater effect on the SBP of patients compared to Sotagliflozin. This reduction in SBP was observed across the patient population. The mean reduction was found to be -2.86 mmHg (P < 0.00001) (Fig 4). None of the included studies mentioned changes in diastolic blood pressure (DBP) in patients receiving Bexagliflozin.

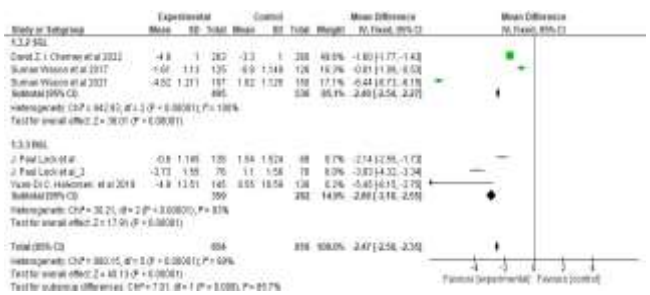

Fig. 4. Effect of SGL Vs BGL on SBP

- *Safety Data:*

In general, both Sotagliflozin (SGL) and Bexagliflozin (BGL) were well tolerated in the studies analysed. The analysis revealed that both drugs tended to cause certain side effects, which included Hypoglycaemia, Urinary tract infections (UTI), and genital mycotic infections.

Regarding genital mycotic infections, SGL was associated with a higher risk (RR: 2.14), indicating that this side effect occurred more frequently in patients receiving SGL compared to those receiving BGL, where the Risk Ratio was 0.46 (Fig 5A)

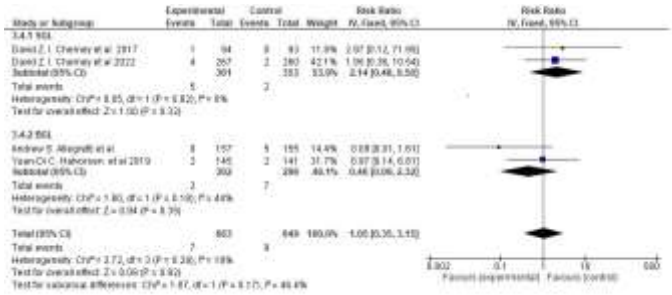

Fig. 5A. Incidence of Genital Mycotic Infection

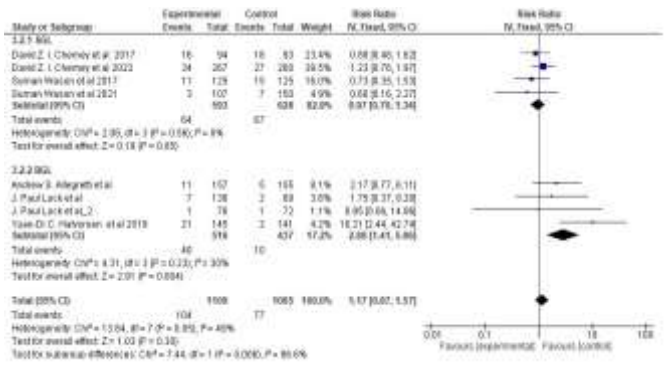

Fig. 5B. Incidence of UTIs

Conversely, UTIs were more commonly observed in patients receiving BGL, as it had an RR: of 2.88, while SGL had an RR: of 0.97 for this side effect (Fig 5B).

Hypoglycaemia, on the other hand, was found to occur almost equally in both drug groups, with SGL having an RR: of 1.05 and BGL having an RR: of 0.98.(Fig 5C)

Fig 5A- Incidence of Genital Mycotic Infection Fig 5A- Incidence of Genital Mycotic Infection Fig 5A- Incidence of Genital Mycotic Infection.

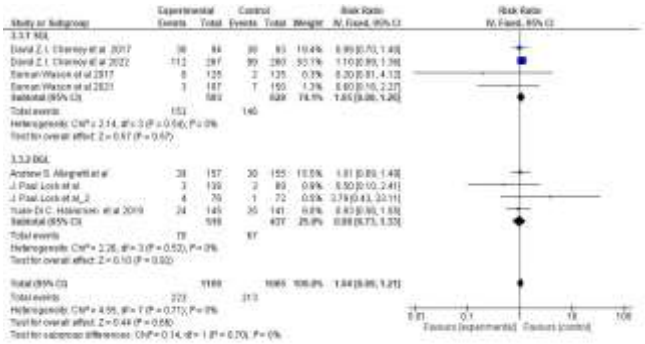

Fig. 5C. Incidence of Hypoglycemia

IV. DISSICUSION

This meta-analysis is registered with Prospero under the ID of CRD42023431893.

Type 2 diabetes mellitus is a progressive systemic disorder characterized by elevated blood sugar levels resulting from dysfunction in both pancreatic β cells and α cells and insulin resistance in peripheral tissues. [8] Current methods used to combat this condition primarily focus on enhancing the glucose metabolism of pancreatic β cells to increase insulin production. However, there is growing interest in SGLT inhibitors, which facilitate Urinary Glucose Excretion (UGE). The advantage of reducing glucose levels without relying on insulin action or burdening β cells has been emphasized as an effective approach to attenuate glucose toxicity and combat chronic hyperglycemia. [11]

Sotagliflozin (LX4211) is a dual SGLT1 and SGLT2 inhibitor. Sotagliflozin slows glucose absorption after meals by blocking SGLT1 in the gastrointestinal tract and increasing glucosuria by targeting SGLT2 in the kidney. [10] In the context of glycemic management, Sotagliflozin was reported to be able to lower HbA1c levels for a brief period, after which the reductions did not approach significance, i.e., there was no meaningful change with the 200 mg dosage, as demonstrated by David et al 2022 [29]. They found that mean changes in HbA1c from baseline were not significantly different between Sotagliflozin and placebo at week 52 in the whole population. This was in line with the data derived from selective inhibitors [14]. Julio Rosenstock et al. [13] reported that Sotagliflozin, by virtue of its SGLT1 inhibition, has demonstrated persistent decreases in postprandial glucose (PPG) levels following an oral glucose challenge or meal. This characteristic could be particularly beneficial for patients with type 2 diabetes and compromised renal function. The dual inhibition of both SGLT1 and SGLT2 may lead to a reduction in A1C levels with less reliance on renal glucose excretion compared to using SGLT2 inhibition alone. This suggests that Sotagliflozin's unique

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mechanism of action holds promise for improving glycemic control in diabetic patients with kidney issues. [13].

Sotagliflozin's additional benefits in providing cardiovascular and renal protection have recently received notice. Notably, Bhatt et al. [12] observed that, when compared to the placebo group, the use of Sotagliflozin before or soon after hospital discharge significantly decreased the overall number of cardiovascular-related mortality, hospitalizations for heart failure, and emergency visits in Type 2 DM patients. Furthermore, Julio Rosenstock et al [13] reported that BP changes with Sotagliflozin therapy were equivalent to approved antihypertensive medications. Interestingly, Bhat et [12] colleagues discovered that the percentage of patients who suffered hypotension was greater with Sotagliflozin than with the placebo.

In terms of safety, Sotagliflozin was shown to be usually well tolerated orally. Sotagliflozin predisposed the patients to diarrhoea, diabetic ketoacidosis, and genital mycotic infections. As noted by David et al 2017 [28] - Genital mycotic infections were seen more frequently in the Sotagliflozin groups than in the placebo groups - the elevated UGE seems to have enhanced the frequency of Genital mycotic infection. Glycosuria is also coupled with osmotic diuresis. Excess urine volume appears to level out at 200-600ml per day with continuous SGLT2 inhibition [11]. This, in turn, may lead to issues associated with volume depletion. Hypoglycemia is typically not associated with the use of SGLT2 inhibitors, either in patients with T2DM or in nondiabetic individuals [15]. Furthermore, SGLT inhibitors are not associated with hypoglycemia when combined with other antihyperglycemic agents that do not raise this risk, such as metformin or DPP4 inhibitors [15].

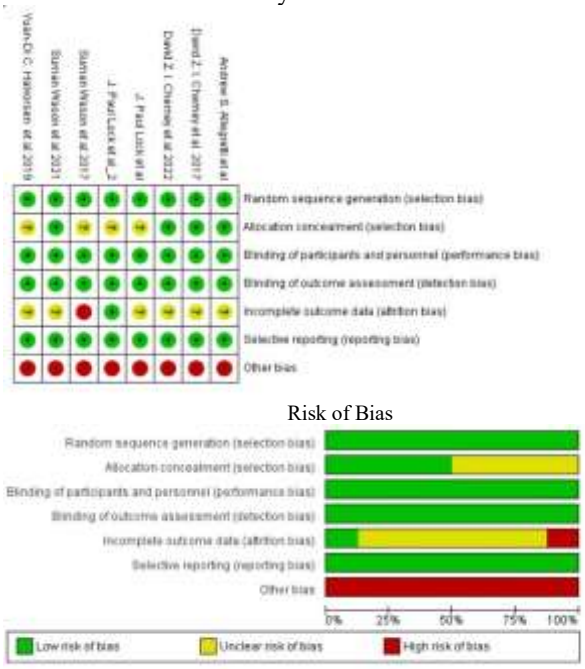
Bexagliflozin is a highly potent SGLT2 inhibitor known for its strong selectivity for the SGLT2 transporter. SGLT2 inhibitors effectively reduce hyperglycaemia in individuals with type 2 diabetes by facilitating the movement of glucose from the bloodstream to the urine. [16] In terms of managing blood sugar levels, Bexagliflozin has demonstrated a long-lasting effect on HbA1c levels in patients. It has been shown to be more effective than both glimepiride and sitagliptin in various research studies. [17] [18] A study conducted by Yuan-Di Halvorsen et al. [18] revealed that Bexagliflozin was less effective than glimepiride at Week 6 of the research, but its activity improved and surpassed glimepiride from Weeks 24 to 96. This suggests that the drug's efficacy increased throughout the study. Furthermore, Bexagliflozin was seen to be beneficial in managing glycemia in individuals with impaired renal function, as observed in Andrew S. Allegretti et al [33].

SGLT2 inhibitors may also effectively reduce the risk of major cardiovascular adverse events (AEs) [19]. Multiple studies have observed reductions in systolic blood pressure (SBP) in patients during their research. In particular, Yuan-Di Halvorsen et al [34]. reported a substantial decrease in SBP with the use of Bexagliflozin. Furthermore, the same study by Yuan-Di Halvorsen et al. [34] noted various changes in haematological parameters during the treatment period with Bexagliflozin. There was an increase in haemoglobin levels, erythrocyte count, and haematocrit, along with a decrease in platelet count. These findings were observed as a class effect, possibly indicating an increase in erythropoietin production among SGLT2 inhibitors [20].

Additionally, Bexagliflozin was found to produce approximately equal increases in both high-density lipoprotein (HDL) and low-density lipoprotein (LDL) concentrations [23]. Although these increases are relatively small, they are consistent with similar findings reported by other members of the SGLT2 class, several of which have reported beneficial cardiovascular outcomes [22]. This indicates that SGLT2 inhibitors, such as Bexagliflozin, might yield beneficial impacts on cardiovascular well-being.

Also, there was an observed decrease in body weight, in line with the typical caloric wasting associated with SGLT2 inhibitors [33]. Lock JP et al [21] found that Bexagliflozin exhibited superiority over glimepiride in reducing body mass among subjects who were overweight or obese at the start of the study. Additionally, Yuan-Di Halvorsen et al (BGL Vs Sitagliptin) [23] observed elevated serum magnesium levels in the Bexagliflozin group, a commonly observed phenomenon within this class of medications. Conversely, serum uric acid levels were found to be decreased in the same study, which is a standard effect seen among SGLT2 inhibitors [24].

Regarding adverse effects, the most frequently reported treatment-emergent adverse events (TEAEs) included nasopharyngitis, urinary tract infection (UTI), hypoglycaemia, and influenza [21]. The presence of volume depletion was also relatively common, possibly attributed to the anticipated osmotic diuresis caused by SGLT2 inhibition. [33]



V. CONCLUSION

This meta-analysis demonstrates that Bexagliflozin (20 mg) is more effective in managing Type 2 Diabetes mellitus compared to Sotagliflozin (200 mg) in several key aspects. Bexagliflozin exhibited significant reductions in HbA1c levels, Fasting Plasma Glucose (FPG), and Systolic Blood Pressure

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(SBP). Notably, Bexagliflozin's impact on HbA1c levels was more immediate and continued to show meaningful results up to and beyond the 24-week mark; unlike Sotagliflozin whose impact eventually stagnated.

Furthermore, Bexagliflozin displayed greater efficacy in reducing the Fasting Plasma Glucose of patients compared to Sotagliflozin. It also demonstrated superior results in reducing SBP, whereas Sotagliflozin did not lead to any significant changes in this regard. However, it is worth noting that Sotagliflozin use was associated with a greater loss of body weight.

When considering safety, Bexagliflozin emerged as the more favorable option as it showed a lower incidence of adverse events, including Hypoglycemia and Genital Mycotic Infections.

In summary, this meta-analysis concludes that Bexagliflozin offers superior management of Type 2 Diabetes Mellitus due to its enhanced glycemic control and reduced incidence of adverse events.

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