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Research Article

Effects of SGLT2 Inhibitors Compared with Sulfonylurea on Glycaemic Control and Cardiovascular Risk Reduction in Asia: Meta-Analysis

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ABSTRACT

International guidelines recommend using Sodium-Glucose Transporter 2 Inhibitors (SGLT2is) for Type 2 Diabetes Mellitus (T2DM) patients. However, there are possible disparities in glycaemic control outcomes among various races and ethnicities. Meanwhile, sulfonylurea is often administered as oral antidiabetic medications in Asia. This study examines the glycaemic control and cardiovascular risk components of SGLT2 inhibitors and sulfonylurea in Asian adults with T2DM. Protocol CRD420234480943 is registered with Prospero. Until February 15, 2024, PubMed, CENTRAL, and EMBASE were searched for pertinent papers. The primary outcome of this Asian T2DM study is the reduction of HbA1c. Secondary outcomes include fasting plasma glucose level, blood pressure, cholesterol profile, and anthropometric measurements. The RoB2 tool assessed bias risk, and Review Manager 5.3 synthesized data. The GRADE framework assessed certainty. Seven articles containing 890 participants were chosen for inclusion. The data analysis showed no statistically significant difference in the primary outcome of HbA1c between SGLT2is and sulfonylurea (MD = 0.06%; 95%CI = -0.13%-0.24%), with low certainty. The subgroup analysis of HbA1c showed a preference for dapagliflozin (MD = -0.36%; 95%CI = -0.63 to -0.08%). Secondary outcomes analysis indicates that SGLT2is have a more favorable effect on improving blood pressure, all anthropometric measurements, and High-Density Lipoprotein (HDL) level. In conclusion, glycaemic control shows no difference between SGLT2is and sulfonylurea. However, SGLT2is can enhance cardiovascular risk reduction. To address the low level of certainty in the data, more research is needed on SGLT2is dosage, type, and duration, especially in Asia.

Keywords:
Asia; Cardiovascular Risk; Glycaemic Control; Meta-Analysis; SGLT2 Inhibitors; Sulfonylurea

1. INTRODUCTION

The type 2 diabetes mellitus (T2DM) prevalence rises annually. Three Asian countries had the highest prevalence of diabetes in 2021[1]. Effective management of T2DM is essential in Asian populations to reach glycaemic control goals and avoid complications. Sodium-Glucose Transporter 2 inhibitors (SGLT2is) like empagliflozin, dapagliflozin, ertugliflozin, canagliflozin, and sotagliflozin are oral antidiabetic medications that work by blocking the glucose reabsorption via proximal renal tubule, resulting in higher glucose elimination through urine[2], and this pharmacology class is available in Asia, and various

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international guidelines have recommended the use of this class[3–5]

Studies showed the efficacy of SGLT2is as an additional treatment to metformin in T2DM compared with sulfonylurea[6,7]. A 104-week Randomized Controlled Trial (RCT) comparing the effectiveness of empagliflozin and glimepiride in T2DM patients with uncontrolled blood sugar levels demonstrated that empagliflozin was more effective in decreasing HbA1c levels[7]

It is vital to consider the impact of SGLT2is on the Asian population due to potential variations in glycaemic control effects across different races and ethnicities. An observational study in the United Kingdom revealed variations in glycaemic control across individuals of white, black, and Asian ethnicities[8]. Genetic, economic, urbanization, and lifestyle factors of Asians might contribute to the glycaemic control [9]. Thus, research is required to assess the efficacy of SGLT2is in glycaemic control, specifically in Asians

Meanwhile, sulfonylurea is an old and prevalent antidiabetic group in Asia. It is recorded that 80% of diabetes patients live in low- and middle-income countries. Therefore, using metformin and sulfonylurea, which are relatively more affordable, is included in the mainstay program for treating T2DM[10]. Sulfonylurea is commonly prescribed oral antidiabetic agents in low- to middle-income countries in Asia, and they are considered essential in various countries, including those in the Southeast Asian region[11]. Thus, this study aims to investigate the efficacy of SGLT2 inhibitors and sulfonylurea in lowering HbA1c levels in Asian individuals with T2DM. Previously, no meta-analysis compared the efficacy of SGLT2is and sulfonylurea on glycaemic control, notably in Asia. Some of the RCTs conducted in Asia produced contradictive results on HbA1c[6,12–17]. Based on the goals of controlling diabetes from various diabetes guidelines, it is essential to manage diabetes with glycaemic control and cardiovascular risks taking into account[2,3]. Thus, this study evaluates the quality, effect size, and certainty level of evidence regarding the use of SGLT2 inhibitors against sulfonylurea on glycaemic control and cardiovascular risk components (anthropometric measurements, blood pressure, and lipid profile) in Asian patients with T2DM, in accordance with the goals of controlling diabetes mellitus.

2. METHODS

The protocol has been registered with Prospero under registration number CRD420234480943. The meta-analysis is reported following the PRISMA criteria.

2.1. Searching Strategies

The study searched PubMed, CENTRAL, and EMBASE for relevant papers until February 15, 2024. A citation search was conducted to reduce the likelihood of publication bias. If clarification is needed for the author's data, a conversation with the authors was conducted via email. The keywords for the CENTRAL and PubMed databases were initially updated in the MeSH database. Additional synonyms were included to enhance the search sensitivity based on the terms in the title or abstract. For the Embase database, keywords were mapped to Emtree terms, and synonyms in the title/abstract were incorporated. We only considered studies with an RCT design and utilized keywords per Cochrane's recommendations. To specify the criteria for the Asia population, the text word menu was used to narrow down the search. There were no restrictions in terms of language or the date of publication.

2.2 Selection of Studies

The research selection method was determined by eligibility criteria following the PICO framework and RCT study design. This study focuses on Asian patients with T2DM. This study's intervention criteria included all SGLT2 inhibitors, compared to the sulfonylurea. This study primarily evaluates changes in HbA1c as the primary outcome. The secondary outcomes being evaluated include alterations in Fasting Plasma Glucose (FPG) levels, blood pressure readings, cholesterol levels, and anthropometric measurements or quantitative non-invasive assessments of the body, such as changes in body weight, waist circumference, and Body Mass Index (BMI) [18]. The list of studies from the database was transferred into the Zotero program. After deduplicating papers, FC and RS screened and picked studies. Discussions continued until consensus was achieved in the event of conflicting opinions. The study selection process utilized the Covidence tool, accessible at https://www.covidence.org/.

2.3 Data Extraction

FC and RS independently extracted data from the papers included in the study. The retrieved data consisted of characteristics of each study, assessed outcomes, and risk of bias assessment. Regarding studies with a broader population (Hollander 2018), data extraction was done by checking Asian data in the supplementary file. The RoB2 tool helped evaluate the risk of bias. A consensus was reached after discussions were made. All research data in this study is continuous.

2.4 Data Synthesis

The continuous data synthesis results are displayed as the Mean Difference and a 95% Confidence Interval (95%CI). Heterogeneity was

evaluated using the I^2 method to show the heterogeneity percentage. Continuous data were synthesized using the Inverse Variance statistical methods. A fixed effect analysis model was applied when the variation between studies was slight (I^2<50%), while the random effect method was used when the variation was considerable (I^2≥50%). The results were presented in a forest plot, and the analysis was performed using the Review Manager (RevMan) 5.3 tool. Sensitivity analysis was conducted to test robustness without high risk of bias articles. This study evaluates the certainty of the primary outcome result using the GRADE framework.

3. RESULTS AND DISCUSSION

3.1 Results

Five hundred sixty-four articles were obtained by searching three databases and completing citation searches. After removing duplicates, 418 publications were reviewed based on title/abstract, and 399 articles were excluded due to different populations (24 articles), different interventions (48 articles), different comparisons (109 articles), different outcomes (131 articles), and non-RCT design (87 articles). Subsequently, 19 articles were reviewed based on full text. Seven papers with N = 890 participants were selected for inclusion after removing 12 articles, as shown in Figure 1. From the characteristics of the included studies (Table 1), the included studies had follow-up durations ranging from 24 to 104 weeks, and all participants had T2DM in Asia. The Hollander 2018 trial included participants from various continents, but we only considered the results from the Asian subgroup. Several SGLT2 inhibitors were studied, including ertugliflozin, dapagliflozin, empagliflozin, tofogliflozin, and canagliflozin, with doses of glimepiride ranging from 0.5 to 4 mg per day as the comparison.

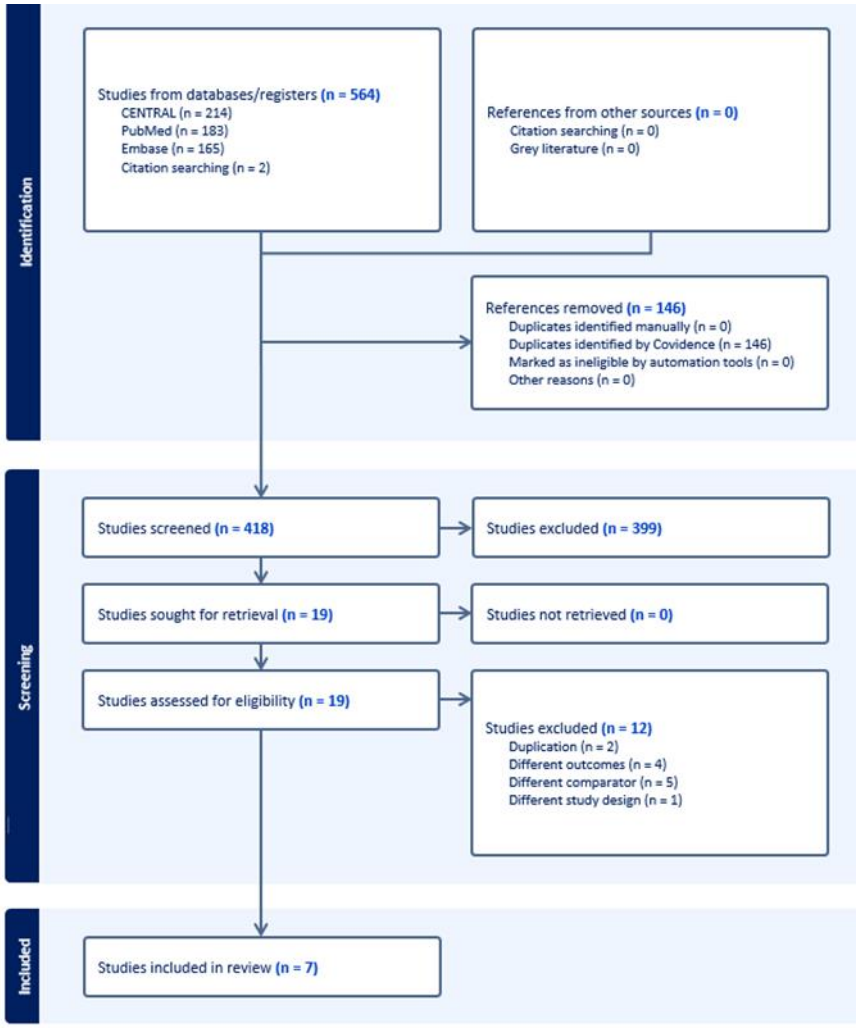


Figure 1. PRISMA Flowchart. The search process resulted in 564 articles. Furthermore, 418 articles went through the screening process, and in the end, seven articles were included in the meta-analysis.

Table 1. Characteristics of Included Studies

Trial	Asian Population Size (N)	Clinical Trial Registry	Intervention	Comparator	Follow-Up Duration	Population	Outcomes
Hollander 2018[6]	198*	NCT01999218	Ertugliflozin 5 and 15 mg	Glimepiride titrated from 1 mg	52 weeks	T2DM, uncontrolled glycemic on metformin	HbA1c
Kinoshita 2020[12]	65**	UMIN 000021291	Dapagliflozin 5 mg	Glimepiride 0.5 – 1 mg	28 weeks	T2DM and NAFLD	BMI, height, lipid and glucose parameters, blood pressure, renal and liver function, adverse events
Kitazawa 2020[13]	64	UMIN000026161	Tofogliflozin 20 mg	Glimepiride 0.5 mg	24 weeks	T2DM on metformin and DPP-4 Inhibitors	Body fat, BMI, body weight, abdominal circumference, glucose metabolism variables, blood pressure, kidney and liver functions, adverse events
Park 2022[14]	124	NCT02564926	Dapagliflozin 10 mg	Glimepiride 1-2 mg	52 weeks	T2DM, uncontrolled glycemic on metformin	Body fat mass, anthropometric measurement, glycemic control, blood pressure, adiponectin, hs-CRP, adverse events
Tanaka 2020[15]	233	UMIN000017669	Canagliflozin 100 mg	Glimepiride 0.5 mg	24 weeks	T2DM and stable CHF	NT-proBNP level, vital signs, glycemic control, estimated plasma volume, echocardiographic measures, NYHA functional classification, CHF-related quality of life, and adverse events
Khunti 2015[7,17]	166	NCT01167881	Empagliflozin 25mg	Glimepiride 1-4 mg	104 weeks	T2DM, as metformin add-on	HbA1c, body weight, and hypoglycemia
Takeshita 2022[16]	40	NCT02649465	Tofogliflozin 20 mg	Glimepiride 0.5 mg	48 weeks	T2DM and NAFLD	Histological score of NAFLD development, glucose metabolism, serum liver-related markers, body compositions, oxidative stress markers, lipid profiles, and cytokine levels

*) Specific data on Asia population, with total population = 1326
**) Specific data in dapagliflozin vs. glimepiride
T2DM = Type 2 Diabetes Mellitus; HbA1c = glycated haemoglobin; NAFLD = Non-Alcoholic Fatty Liver Disease; BMI = Body Mass Index; hs-CRP = High-Sensitivity C-Reactive Protein; NT-proBNP = N-terminal Prohormone of Brain Natriuretic Peptide; CHF = Chronic Heart Failure

Results from the risk of bias assessment (Figure 2) conclude that out of the seven trials analyzed, two had a high risk of bias, and the other five had a low risk of bias. Two trials, Khunti 2015 and Takeshita 2022, used intention-to-treat analysis, whereas the other five used per protocol analysis. Therefore, it is essential to thoroughly examine deviations from the intended treatment and missing data for the per-protocol analysis. Thus, two trials with a high risk of bias did not undergo extra analysis to address this deviation. The substantial risk of bias in section D3 results from missing data and the lack of additional studies to address this issue.

Study ID	Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall
Hollander et al., 2018	Ertugliflozin	Glimepiride	HbA1c	+	+	+	+	+	+
Kinoshita et al., 2020	Dapagliflozin	Glimepiride	HbA1c	+	-	+	+	+	-
Kitazawa et al., 2020	Tofogliflozin	Glimepiride	HbA1c	+	+	+	+	+	+
Park et al., 2022	Dapagliflozin	Glimepiride	HbA1c	+	-	-	+	+	-
Tanaka et al., 2020	Canagliflozin	Glimepiride	HbA1c	+	+	+	+	+	+
Khunti et al., 2015	Empagliflozin	Glimepiride	HbA1c	+	+	+	+	+	+
Takeshita et al., 2022	Tofogliflozin	Glimepiride	HbA1c	+	+	+	+	+	+

+ Low risk
! Some concerns
- High risk
D1: Randomisation process
D2: Deviations from the intended interventions
D3: Missing outcome data
D4: Measurement of the outcome
D5: Selection of the reported result

Figure 2. Results of Risk of.0 Bias Assessment**.** Regarding the HbA1c primary outcome, two out of seven articles have a high risk of bias due to falls in D2 and D3 components. HbA1c = glycated hemoglobin.

The data synthesis findings generated with the RevMan tool showed no significant difference in the primary outcome of HbA1c between SGLT2is and sulfonylurea, with MD = 0.06%; 95%CI = -0.13 – 0.24%, and substantial heterogeneity (I^2 = 63%), as seen in Figure 3. A subgroup study of Asian individuals with T2DM who received metformin add-on therapy showed comparable findings, with MD = 0.04%; 95%CI = -0.18 – 0.25%), and I^2 = 58%. Subgroup analysis results for follow-up durations of ≤48 weeks and >48 weeks also showed comparable findings: MD = 0.14%; 95%CI = -0.14 – 0.42%; I^2 = 58% and MD = -0.00; 95%CI = -0.26 – 0.25%; I^2 = 66% respectively. However, the subgroup analysis comparing dapagliflozin and glimepiride favored SGLT2is with MD = -0.36%; 95%CI = -0.63 - -0.08%, and a more homogeneous conclusion (I^2 = 0%), as seen in Figure 4. These findings differ from the sensitivity analysis results that excluded high-risk bias trials. The results showed a preference for glimepiride with MD = 0.19, 95%CI = 0.07 – 0.31%, and I^2 = 0%. The Takeshita 2023 study was excluded from the HbA1c data synthesis due to the presentation of mean difference (%) and interquartile range (IQR) results, making them incompatible for synthesis.

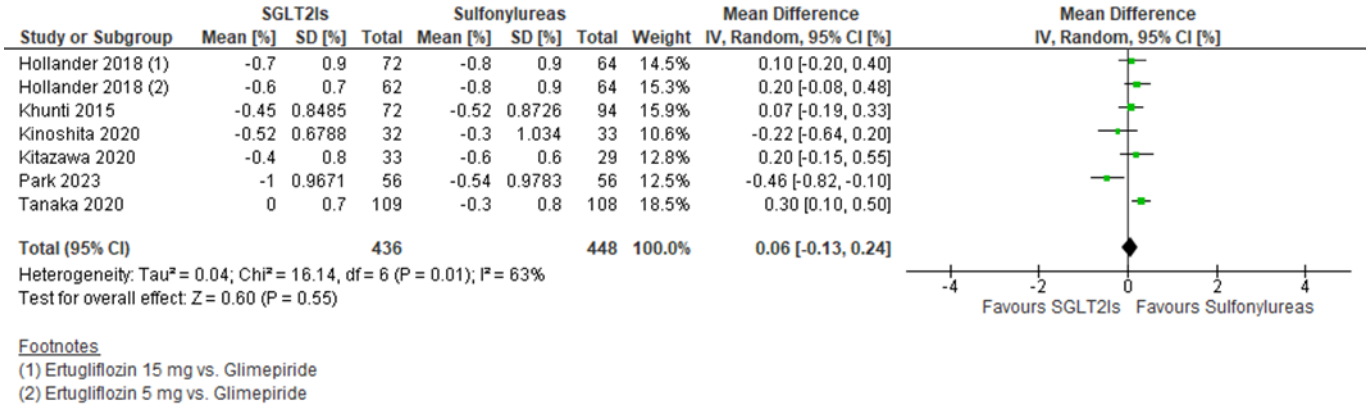


Figure 3. Forest Plot of HbA1c Outcome. SD = Standard Deviation, IV = Inverse Variance, 95%CI = 95% Confidence Interval, SGLT2is = Sodium-Glucose Transporter 2 Inhibitors.

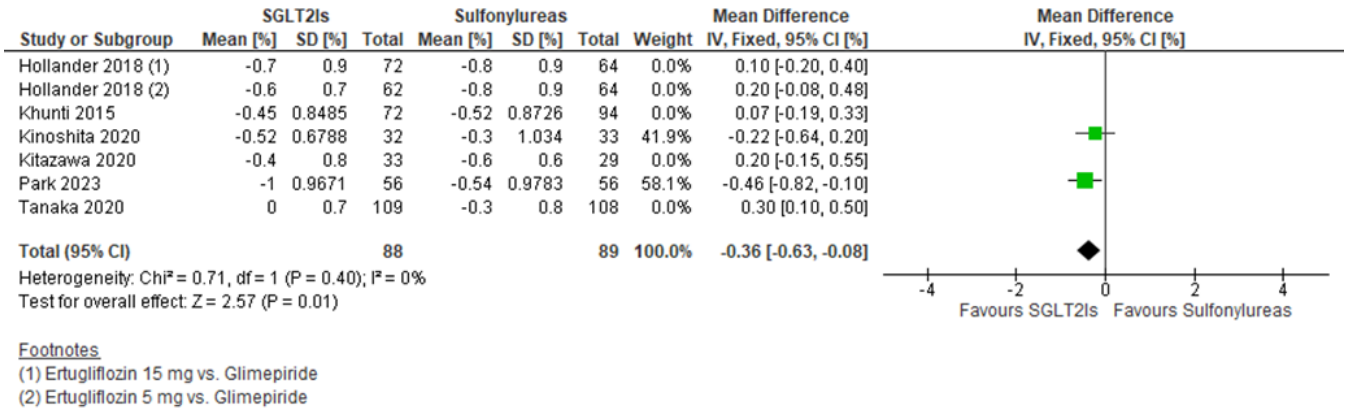
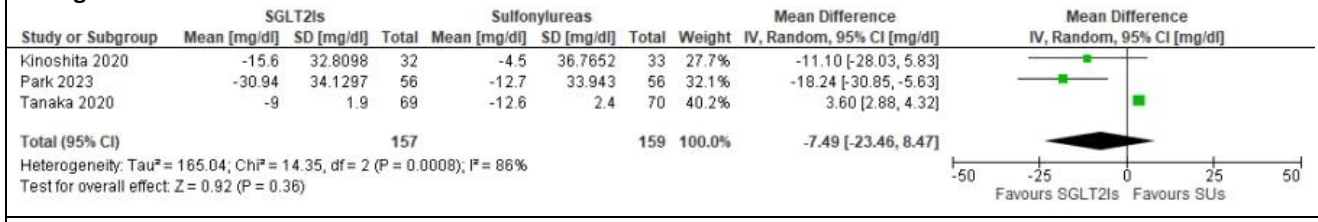


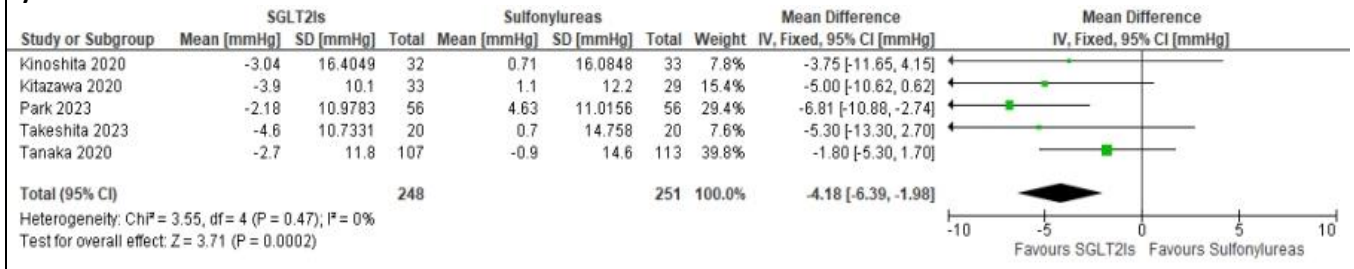
Figure 4. HbA1c Primary Outcome Subgroup Analysis on Dapagliflozin vs. Glimepiride. SD = Standard Deviation, IV = Inverse Variance, 95%CI = 95% Confidence Interval, SGLT2is = Sodium-Glucose Transporter 2 Inhibitors

Secondary outcomes data synthesis shows that SGLT2is have a better impact on improving Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), body weight, BMI, waist circumference, and High-Density Lipoprotein (HDL) level, compared to glimepiride, as seen in Figure 5. Meanwhile, SGLT2is do not impact other secondary outcomes, such as FPG and Low-Density Lipoprotein (LDL) levels. High heterogeneity results were found in FPG level, body weight, and waist circumference outcomes. Thus, the random model was used to synthesize these outcomes.

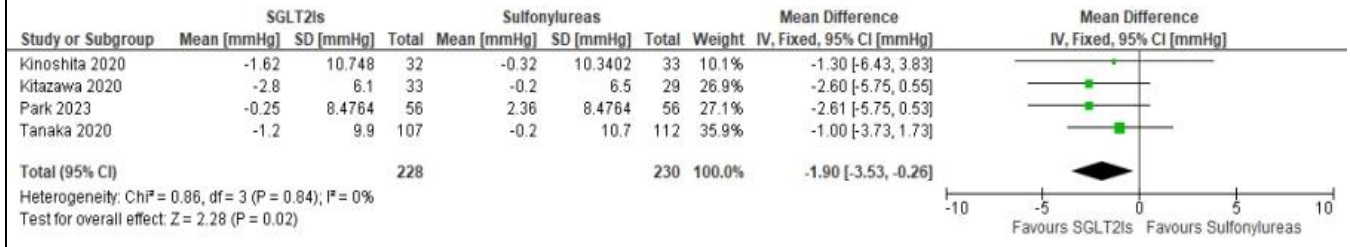
Fasting Plasma Glucose:



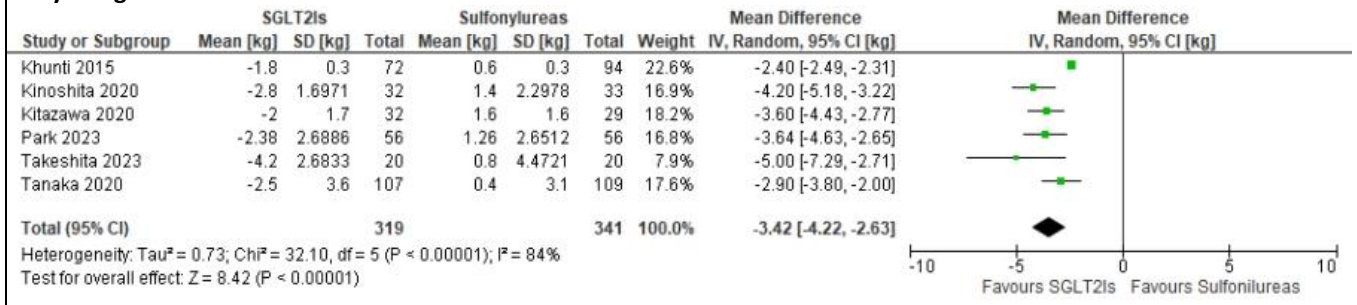
Systolic Blood Pressure:



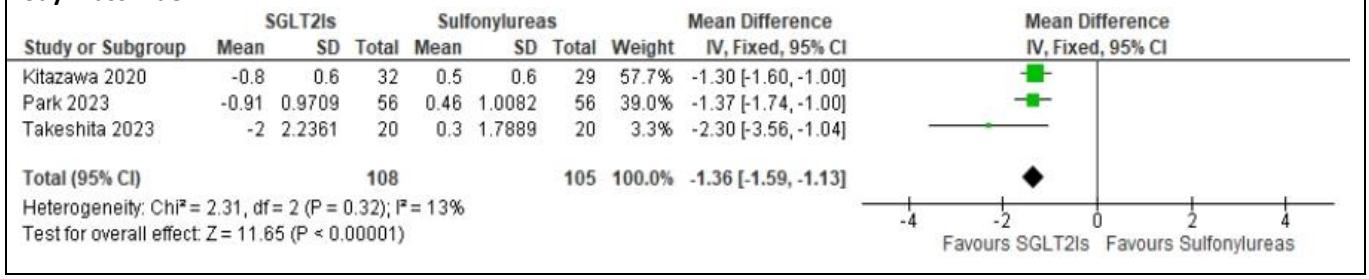
Diastolic Blood Pressure:



Body Weight:



Body Mass Index:



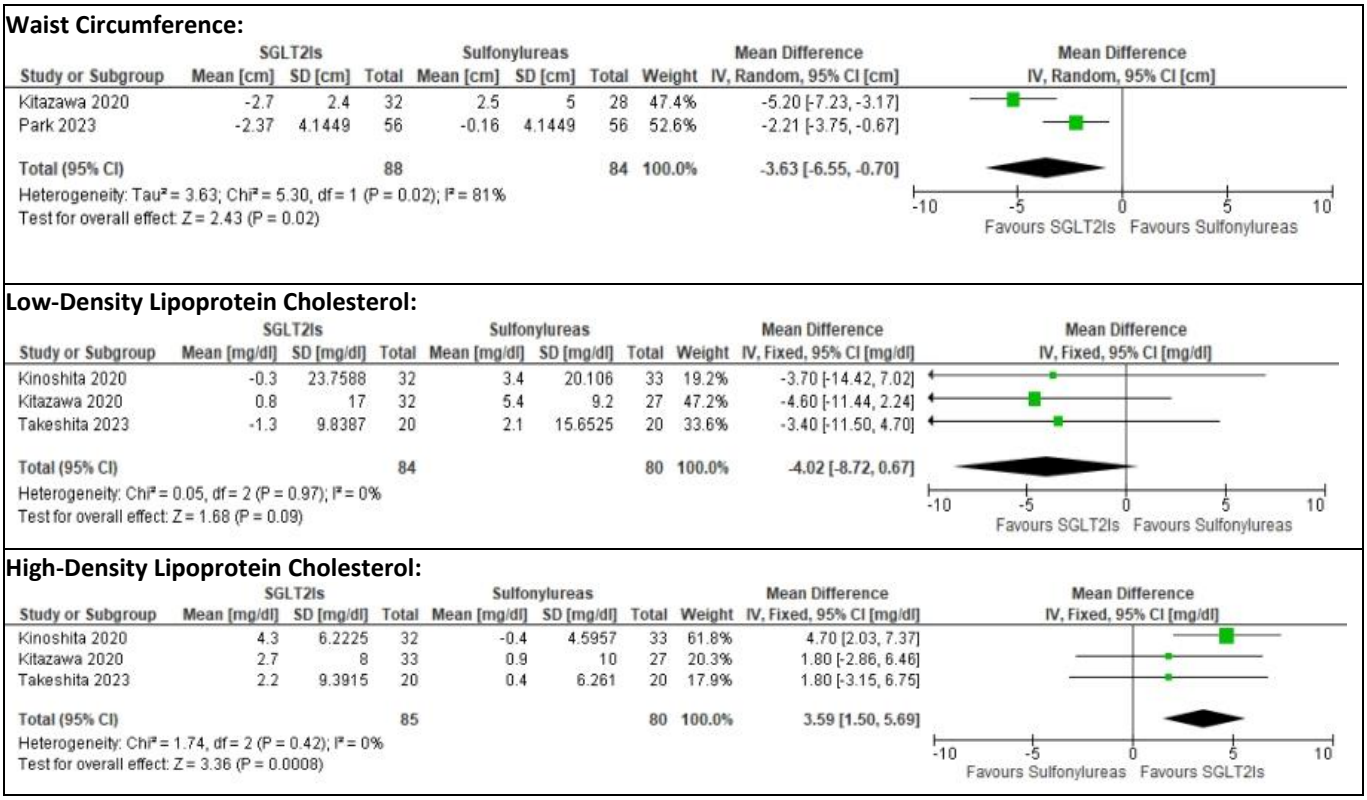


Figure 5. Forest Plot of Secondary Outcomes. SD = Standard Deviation, IV = Inverse Variance, 95%CI = 95% Confidence Interval, SGLT2 is = Sodium-Glucose Transporter 2 Inhibito

The GRADE analysis indicates that the trials have a low level of certainty because of the likelihood of bias, inconsistency, and imprecision for the primary outcome of HbA1c. The risk of bias resulted from RoB2 data extraction, while inconsistency is due to significant heterogeneity and imprecision caused by a wide range of confidence interval levels. No indirectness and publication bias risks were found from this meta-analysis's evidence.

3.2 Discussion

This meta-analysis of metformin add-on therapy interventions shows no significant difference in decreasing HbA1c levels between SGLT2is and sulfonylurea. This study's results contrast with a previous meta-analysis that included a more extensive and diverse population, consisting of nine trials and 10,974 people. In that analysis, SGLT2is were more effective than sulfonylurea in reducing HbA1c levels[19]. Similar to other glycemic control markers such as FPG, past meta-analyses have shown conflicting results compared to our current meta-analysis[19,20]. Past and recent meta-analyses exhibited significant heterogeneity in the primary outcome of HbA1c. Interestingly, subgroup analysis on treatment duration revealed contrasting results. The previous meta-analysis indicated a more significant improvement in HbA1c in the SGLT2is group after 2-4 years, with insignificant effects at one year. Moreover, a more extended treatment duration was associated with a more significant difference in HbA1c from both groups[19]. Multiple meta-analyses in worldwide populations demonstrate a consistent pattern: the longer SGLT2is are used, the more effective they are compared to sulfonylurea. Sulfonylurea offers more benefits in the short term but not in the long run[20,21]. Interestingly, the sensitivity analysis results in this study demonstrated improved HbA1c outcomes in the sulfonylurea group. This is feasible because the follow-up time and the highest duration of intervention use are 104 weeks, which is insufficient to observe the long-term effects of the intervention. Therefore, an extended study period exceeding two years is required to keep the impact of utilizing SGLT2is in Asian populations.

Meanwhile, regarding the specific type of SGLT2is, an RCT study compared canagliflozin with glimepiride and found that canagliflozin, particularly at a high dose of 300 mg/day, is more effective in decreasing HbA1c levels[22]. Likewise, an RCT comparing dapagliflozin and glipizide found that dapagliflozin consistently and significantly reduced HbA1c levels better than glipizide over time[23,24]. Consistent with a recent meta-analysis, dapagliflozin had superior HbA1c outcomes to the sulfonylurea group in the sub-group analysis. Additional study is required to investigate the benefits of different types of SGLT2 inhibitors and their dosages on enhancing glycemic

control, particularly in Asian people, due to the low availability of clinical studies or randomized controlled trials in this demographic.

The differences in characteristics between global and Asian populations could be the basis for differences in glycaemic control outcomes. Asian people tend to develop diabetes at a younger age and with a lower BMI. Asian communities are more prone to abdominal obesity, have a greater amount of visceral adipose tissue, and lower muscle mass, resulting in higher insulin resistance compared to Western cultures [25]. Aside from genetic traits, the dietary habits of Asians, who primarily consume rice and wheat with high glycaemic indexes, can impact their glycaemic control[26]. Asian individuals exhibit higher plasma glucose levels following an oral glucose tolerance test, suggesting diminished beta cell function in response to insulin resistance compared to non-Asians[27].

Previous meta-analyses with a broader sample demonstrated comparable findings regarding secondary outcomes on SBP, DBP, and body weight[19,20]. SBP, DBP, and body weight improved significantly in the SGLT2is group compared to the sulfonylurea group. SGLT2 inhibitors lower blood pressure through multiple methods. One way is by losing weight. Prior studies indicate that hypertension is correlated with surplus body fat, and decreasing body fat can improve blood pressure.[28,29]. Several randomized controlled trials demonstrate weight loss when using SGLT2 inhibitors, which may lead to a potential decrease in blood pressure[29,30]. Other mechanisms to reduce blood pressure are decreasing sympathetic activity[31], insulin resistance improvement, endothelial function improvement, and natriuresis, resulting in a decrease in sodium content in the muscle[32]. However, there are conflicting research results regarding the relationship between the use of SGLT2 inhibitors and increased natriuresis[33].

Meanwhile, enhancements in anthropometric measures can result from many processes. 1) SGLT2 inhibitors may enhance Adenosine Monophosphate-Activated Protein Kinase (AMPK) and Acetyl-CoA Carboxylase (ACC) phosphorylation in skeletal muscle and elevate Fibroblast Growth Factor 21 (FGF 21) levels in the liver and bloodstream, leading to heightened sympathetic activity in the central nervous system, ultimately boosting energy expenditure and facilitating weight loss[34,35]; 2) SGLT2is can decrease visceral and subcutaneous fat mass by promoting the usage of fatty acids as an energy source[35,36].

This meta-analysis demonstrates that SGLT2is enhanced HDL-C levels compared to sulfonylurea, with no significant impact on LDL-C. A review of 60 randomized controlled trials, including 147,130 patients, revealed that using SGLT2 inhibitors led to elevated total cholesterol, increased LDL cholesterol, improved HDL cholesterol, and reduced triglycerides compared to a placebo. This study is limited by its significant heterogeneity, possibly due to differences in fundamental variables such as gender, age, BMI, ethnicity, type of SGLT2 inhibitor, indication for medication, duration, and dose[37]. Particularly for LDL, different sizes and densities might lead to heterogeneity. Small, low-density LDL particles have a higher risk of causing cardiovascular disease due to their prolonged circulation in the blood, increased ability to penetrate artery walls, and higher susceptibility to oxidation, leading to a more significant potential for atherogenesis[35,37]. In this meta-analysis, synthesizing data on triglycerides and total cholesterol was impossible due to limited studies investigating these components.

The strengths of this meta-analysis are due to the absence of comparable studies in Asia that provide HbA1c data comparing SGLT2is and sulfonylurea, together with investigations of various secondary outcomes to this community. Nevertheless, this meta-analysis is limited by the substantial heterogeneity observed for the primary outcome of HbA1c. Despite attempts at subgroup analysis, the results remain varied, except for the dapagliflozin subgroup, which yielded distinct conclusions. However, this subgroup of dapagliflozin trials contains two studies with a significant risk of bias. The second limitation is that the majority of the studies were carried out in East Asia (Japan and Korea) with some data from Khunti for South Asia, making it challenging to apply the results to other regions of Asia, like Southeast Asia, due to potential racial variations that may impact glycaemic control. The third constraint is the restricted quantity of studies included, which hinders the thorough examination of the dosage, type, and duration impacts of SGLT2is compared to sulfonylurea. The subsequent constraint is the outcomes of the GRADE analysis indicating poor certainty, necessitating additional research to address the third constraint.

4. CONCLUSION

There is no significant difference in glycaemic control measured by HbA1c between SGLT2is and sulfonylurea. However, SGLT2is can improve blood pressure, anthropometric measurements, and HDL levels. Dapagliflozin may offer improved glycemic control results. Thus, SGLT2is are helpful for Asians with T2DM, who experience hypertension, poor HDL, obesity, or overweight. Additional research is required to investigate the impact of dosage, type, and duration of SGLT2is compared to sulfonylurea, especially in Asian populations.

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Authors contribution

FC: Conceptualization, Methodology, Data Collection, Data curation, Formal Analysis, Investigation, Project administrator, Validation, Writing-original draft preparation
RS: Conceptualization, Methodology, Data Collection, Data curation, Formal analysis, Investigation, Supervision, Validation, Writing - review & editing
DLT: Supervision, Writing - review & editing
HS: Supervision, Writing - review & editing

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethics approval

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